

STUDIES IN REACTION MECHANISMS AND MOLECULAR REARRANGEMENTS
&
STUDIES DIRECTED TOWARDS THE SYNTHESIS OF
INSECT SEX PHEROMONES

By
VIDYA BHUSHAN LOHRAY



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DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR
AUGUST, 1983

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INSECT SEX PHEROMONES

A Thesis Submitted
in Partial Fulfilment of the Requirements,
for the Degree of
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By
VIDYA BHUSHAN LOHRAY

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to the

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR
AUGUST, 1983

28 AUG 1984

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Dedicated
to
My Parents

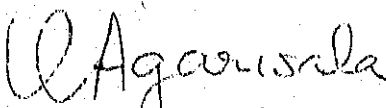
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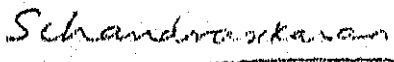
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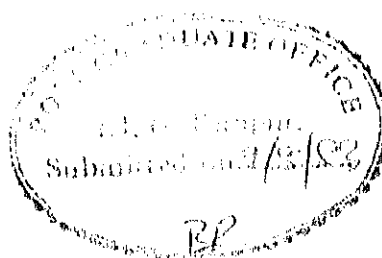
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Ms. Vidya Bhushan Lohray has successfully completed her Ph.D. qualifying examinations in January 1980.


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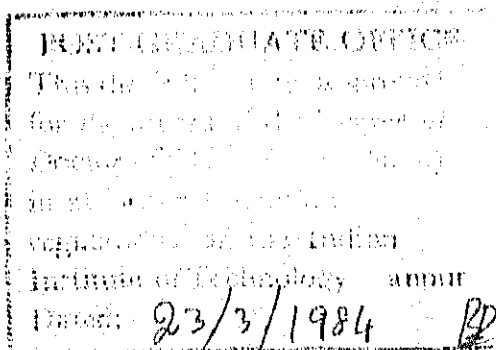
STUDIES IN REACTION MECHANISMS AND MOLECULAR
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has been carried out by Ms. Vidya Bhushan Lohray under my
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for a degree.

S. Chandrasekaran
S. CHANDRASEKARAN
Thesis Supervisor

Kanpur,
August 1983.



STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Professor S. Chandrasekaran.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Vidya Bhushan
VIDYA BHUSHAN LOHRAY

Kanpur
August 1983.

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Acknowledgements are due to my colleagues and friends, past and present, for their delightful company in the lab as well as outside. The help rendered by the staff of the Chemistry Department, Central Library, Low-Temperature Lab and Glass-Blowing is highly appreciated.

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VIDYA BHUSHAN

PREFACE

The thesis entitled: "STUDIES IN REACTION MECHANISMS AND MOLECULAR REARRANGEMENTS & STUDIES DIRECTED TOWARDS THE SYNTHESIS OF INSECT SEX PHEROMONES" consists of two chapters and each chapter has been divided into two sections, Part-A and Part-B.

Chapter I, Part-A of the thesis describes our studies in exploring the mechanism of formation of the cyclic carbonates in the reaction of 4-dimethylaminopyridine (1, DMAP) and acetic anhydride with 1,2-ditertiary diols. The generality of this reaction has been substantiated on the basis of the reactions with a few 1,2-ditertiary diols such as 2,3-dihydroxy-2,3-dimethylbutane (48), 1,1'-dihydroxybicyclohexane (52), 1,1'-dihydroxybicyclopentane (61) and 1-(2'-hydroxypropyl)cyclohexanol (65). It has been observed that the cyclic carbonates are the major products in these reactions, apart from the small amounts of normal acetylation products. A few tertiary alcohols such as 1-methylcyclohexanol (3) and 2-phenylpropan-2-ol (97) were found to give corresponding acetoacetates in addition to simple acetates under the same reaction conditions. Based on the different products isolated in the reactions of these substrates with acetic anhydride and 4-dimethylaminopyridine, reasonable mechanisms have been postulated and examined. The detailed investigations have prompted us to suggest the intermediacy of ketene and diketene in these reactions.

Chapter I, Part-B of the thesis deals with a short synthesis of the seven-membered monoterpene, Karahanaenone (4), an odoriferous constituent of Japanese hop and Cypress oil. The key intermediate 1-(2'-hydroxypropyl)-4-methyl-3-cyclohexenol (20) has been synthesized by the reductive coupling reaction of 4-methyl-3-cyclohexenone (18) and acetone, mediated by low-valent titanium species generated by the reaction of titanium tetrachloride and amalgamated magnesium. The unsymmetrical pinacol 20 underwent a smooth molecular rearrangement with boron trifluoride etherate resulting in the ring expansion to yield Karahanaenone (4). A new methodology has been developed for the synthesis of the useful synthon, 4-methyl-3-cyclohexenone (18), utilizing the methoxyethoxymethyl (MEM) protective group.

Studies directed towards the synthesis of the sex pheromone of cigarette beetle (Lasioderma serricorne F.) forms the subject matter of Chapter II, Part-A. The inherent symmetry possessed by the pheromone, 4,6-dimethyl-7-hydroxy-3-nonanone (1) has been made use of, in devising the synthetic strategy. 1,3-Dimethylindane (27), an important intermediate in the synthesis, has been prepared from benzonorbornadiene (26) in three simple steps. The synthesis of the hydrocarbon 25 has been achieved in six steps from 27, which serves as the key intermediate in the synthesis. In the course of the synthetic efforts, a methodology has been developed for the cis-hydroxylation of olefins under anhydrous conditions using a stable and inexpensive reagent,

cetyltrimethylammonium permanganate.

Chapter II, Part-B consists of our studies which culminated in a simple one-pot α -bromoacetalization of carbonyl compounds. The reaction of carbonyl compounds with phenyltrimethylammonium tribromide (PTT) with excess of ethylene glycol in tetrahydrofuran at room temperature, resulted in the bromination and acetalization in a single step in good yields. The synthetic utility of the α -bromoacetals has been established in the facile synthesis of cyclic 1,3-diketones which are important synthons in organic synthesis. This transformation has been achieved very easily via the formation of olefinic acetals 42 by dehydrobromination, followed by oxymercuration-demercuration to yield hydroxyacetals 43. The hydroxyacetals 43 have been oxidized to the ketoacetals (17, 45) and subsequent hydrolysis has yielded the cyclic 1,3-diketones, 16 and 19.

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CHAPTER I

(PART A)

STUDIES IN REACTION MECHANISMS: FORMATION OF CYCLIC CARBONATES IN THE REACTION OF 4-DIMETHYLAMINOPYRIDINE AND ACETIC ANHYDRIDE WITH 1,2-DITERTIARY DIOLS

I.A.1 ABSTRACT

The reaction of 2,3-dihydroxy-2,3-dimethylbutane with 4-dimethylaminopyridine (DMAP) and acetic anhydride (Ac_2O) in equimolar amounts has been found to give rise to the cyclic carbonate, 2-oxo-4,4,5,5-tetramethyl-1,3-dioxolane along with the normal acetylation products. The generality of the reaction has been tested with a few other 1,2-ditertiary diols such as 1,1'-dihydroxybicyclohexane, 1,1'-dihydroxybicyclopentane and 1-(2'-hydroxypropyl)cyclohexanol. Based on the different products isolated in the reactions of these substrates with Ac_2O /DMAP, reasonable mechanisms have been postulated and examined. A few tertiary alcohols under the same reaction

conditions were found to give acetoacetates in addition to simple acetates. The detailed investigations have prompted us to suggest the intermediacy of ketene and diketene in these reactions.

I.A.2 INTRODUCTION

Dimethylaminopyridine (1, DMAP) has been used as an effective and efficient catalyst in various types of reactions for the last fifteen years.¹ As early as 1967, Litvinenko and Kirichenko found that DMAP resulted in an enormous rate enhancement of ca. 10^4 for the benzoylation of m-chloroaniline, when compared to pyridine.² Later in 1969, Steglich and Höfle described DMAP and 4-pyrrolidinopyridine (2, PPY) as "superlative acylation catalysts" based on their studies in the preparative scale acylations of tertiary alcohols.³

Dimethylaminopyridine can be obtained by reaction of 4-chloropicolinic acid with dimethylaniline followed by decarboxylation.⁴ But, for a technical scale preparation, the facile transformation of 1-(4-pyridino)pyridinium dichloride⁵ with N,N-dimethylformamide is conveniently used.^{6,7}

The utility of dimethylaminopyridine has become so wide that reviewing of the field exhaustively is a difficult task. Therefore, only some important aspects of this versatile reagent will be accounted here.

I.A.2.1 Acylation Reactions Catalysed by Dimethylaminopyridine

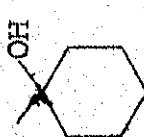
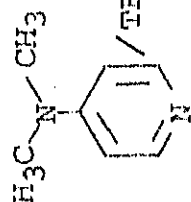
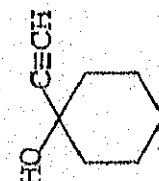
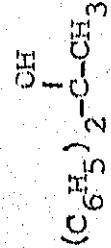


I.A.2.1a Acylation of Alcohols

Dimethylaminopyridine has been extensively used for the acylation of alcohols, especially of sterically hindered secondary and tertiary ones, where the conventional method⁸ using acetic anhydride and pyridine fails. Generally, catalytic amount of DMAP is sufficient for acylation reactions. But in the case of sterically hindered alcohols, an equimolar amount of an auxillary base such as triethylamine (TEA) or pyridine is needed in order to bind the acid formed in the reaction. A few examples of acylation of tertiary alcohols catalysed by DMAP (1) or PPY (2) are listed in Table I.A.1.

It has been observed that acylation of alcohols such as 7 and 8, containing acid-labile functionalities, can be easily achieved in high yields under these mild conditions. In the acetylation of 8, dimethylaminopyridine acts both as the catalyst and the auxillary base. The formation of tert-butyl iso-butyrate and iso-propyl pivalate from 10 and 11, respectively, indicate that despite the steric hindrance of the anhydride, the catalytic effect of DMAP is large enough to be of preparative value.

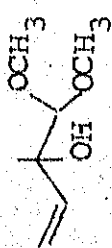
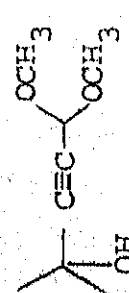
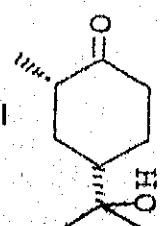
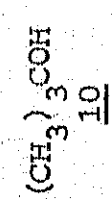
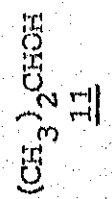

The dialkylaminopyridines 1 and 2 have also been used as catalysts for several formylation reactions using a mixture of formic acid and acetic anhydride.¹ Thus the formylation of carbinol 4 has been carried out at low temperature (at ca. -30 °C),

Table I.A.1 4-Dimethylaminopyridine (DMAP) and 4-Pyrrolidinopyridine (PPY) Catalysed
Acylation of Tertiary Alcohols with Carboxylic Anhydrides

Alcohol	Carboxylic anhydride	Catalyst/ Auxiliary base	Time (h)	Tempe- rature (°C)	Yield (%)	Reference
1	2	3	4	5	6	7
	$(C_6H_5CO)_2O$	 /TEA (DMAP, <u>1</u>)	13	80 [a]	87	3
	$(C_2H_5CO)_2O$	DMAP/TEA	1	24 [a,b]	94	3
	$(CH_3CO)_2O$	 /TEA (PPY, <u>2</u>)	40	24 [a]	92	1
	$(CH_3CO)_2O$	DMAP/TEA	14	24 [a]	80	3

...contd.

Table I.A.1 (contd.)

1	2	3	4	5	6	7
	$(\text{CH}_3\text{CO})_2\text{O}$	PPV/TEA	12	24 [c]	86	9
	$(\text{CH}_3\text{CO})_2\text{O}$	DMAP	0.5	24 [c]	92	3
	$(\text{CH}_3\text{CO})_2\text{O}$	Pyridine	18	110 [e]	81	10
	$(\text{CH}_3)_3\text{COH}$	DMAP	-	24 [d]	-	3
	$[(\text{CH}_3)_3\text{CCO}]_2\text{O}$	DMAP	-	24 [b, f]	-	3
	$(\text{CH}_3\text{CO})_2\text{O}/\text{HCO}_2\text{H}$	DMAP/TEA	1.5	-30 [c]	72	1

[a] without solvent; [b] exothermic reaction; [c] in dichloromethane; [d] in TEA; [e] in toluene; [f] in ether.

with a view to avoiding the decomposition of formic acid to carbon monoxide. It may be mentioned that under these controlled conditions, only mixed anhydride is generated in situ.

However, anhydrides of dicarboxylic acids react with alcohols in the presence of catalytic amounts of DMAP (1) or PPY (2) to form the half esters which are useful for the resolution of racemates.^{11,12} The dimethylaminopyridine catalysis has been extensively utilized for the acylation of sterically hindered hydroxyl groups in carbohydrates,¹³⁻¹⁵ steroids¹⁶⁻²⁰ and prostaglandins.²¹

The enormous increase in the rate of acylation as well as quantitative conversion of unhindered primary and secondary alcohols to their acylated derivatives, with DMAP catalysis has made its use quite attractive. Thus this method has been used for the quantitative determination of hydroxyl groups in alcohols, phenols, glycols and sugars.²² This technique has also been employed in the assay of clindamycin palmitate hydrochloride.²³

Dimethylaminopyridine catalysed acylations are used in the nucleoside chemistry too.^{24,25} Recently, it has been observed that DMAP increases the rate of internucleotide bond formation in the di- and triester method of oligonucleotide synthesis.²⁶ Deoxygenation of ribonucleoside to deoxyribonucleoside has also been achieved using DMAP.²⁷

I.A.2.1b Acylation of Phenols

It has been observed that 4-dialkylaminopyridines 1 and 2 effect a comparable rate enhancement in the acylation of phenols, as in the case of alcohols. Interestingly, sterically hindered phenols like mesitol,¹¹ 2,5-ditert-butylphenol and analogous compounds²⁸ are smoothly transformed to the acyl derivatives in high yields. Similarly, m-cresol can be carbamoylated using dimethylcarbamoyl chloride in quantitative yield employing catalytic amount of DMAP.¹ It has also been reported that 11,12-dihydroglaziovine can be smoothly acylated using this procedure.²⁹ Dimethylaminopyridine has been effectively used in the formylation of sterically hindered phenols where the conventional methods such as Riemer-Tiemann, Gattermann and Duff reactions fail. For example, acylation of 2,5-ditert-butylphenol can be achieved in very good yield using DMAP as catalyst.³⁰ It has also been found to facilitate greatly the transesterification reactions of o-nitrophenylcarbonates.³¹

I.A.2.1c Acylation of Amines

Though the acylation of amines have not been investigated as extensively as those of alcohols and phenols, a few well studied examples are reported in the literature. For example, the kinetics of the benzoylation of m-chloroaniline has been examined in detail³² in the presence of a wide range of amines and the rate constant for the catalysis has been found to follow

the following order: N,N-Dimethylaniline (0.10), Triethylamine (0.072), 2,6-Dimethylpyridine (0.03), Pyridine (1.80), 4-Methylpyridine (10.0) and 4-Dimethylaminopyridine (10,600).

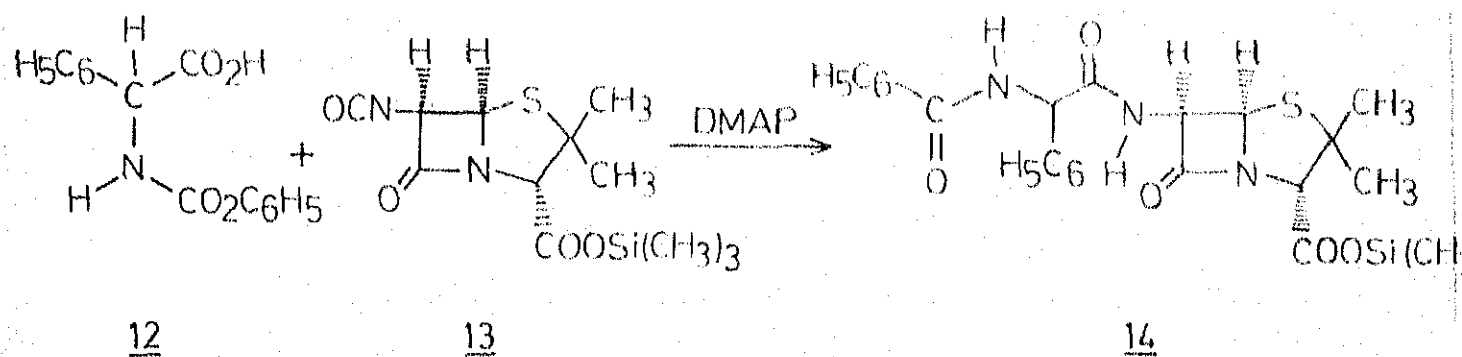
I.A.2.2 Reactions of Isocyanates

Isocyanates react with carboxylic acids to form amides. This reaction is found to be strongly accelerated on replacement of pyridine by DMAP as a catalyst. Thus phenylisocyanate reacts with phenylacetic acid to give the corresponding amide.^{1,33} Similarly, the reactions of trimethylsilyl 6-isocyanatopencillanate (13) with D-N-benzoyloxycarbonyl-2-phenylglycine (12) to give the ampicillin derivative 14 are greatly facilitated by the use of DMAP as catalyst (Scheme I.A.1).³³ Arylisocyanates are found to trimerize on heating with DMAP in ethyl acetate.¹

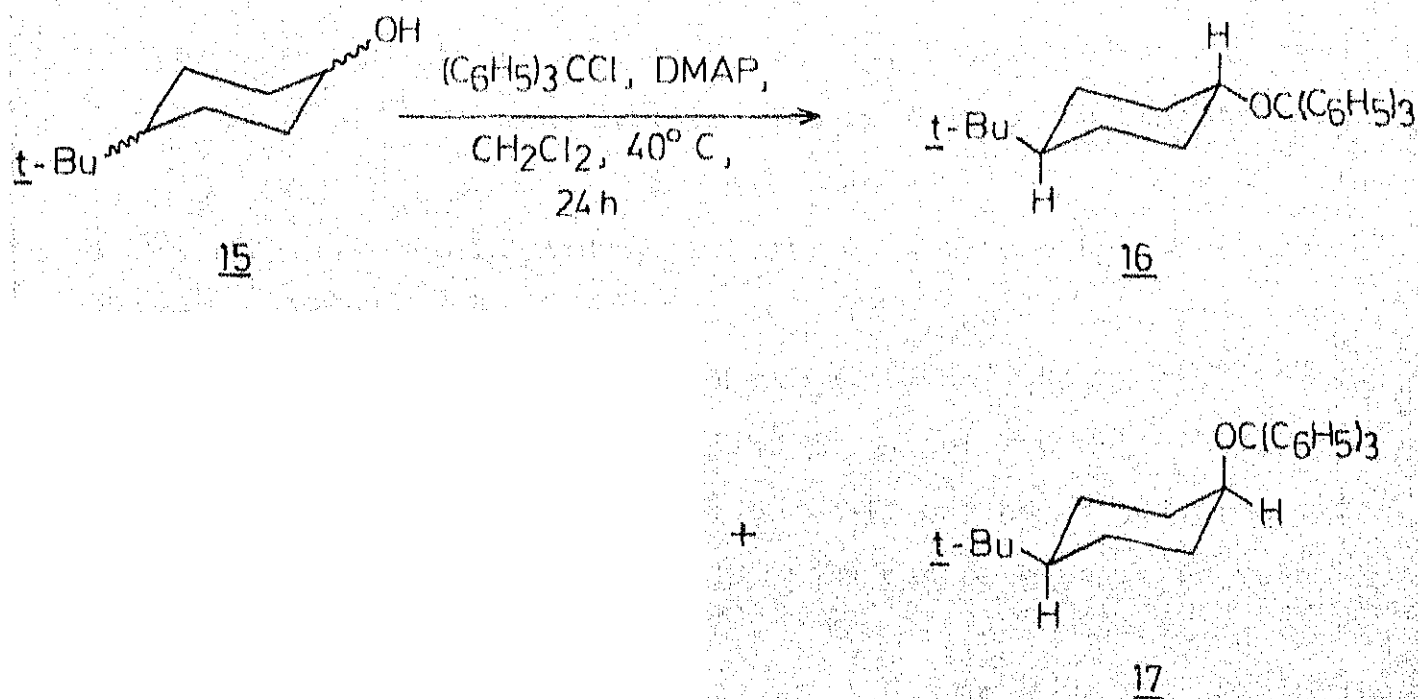
I.A.2.3 Alkylations Catalysed by DMAP

Dimethylaminopyridine has been used as an effective catalyst for alkylation reactions also. For example, tritylation of a mixture of cis- and trans- isomers of 4-tert-butylcyclohexanols 15 can be catalysed by DMAP to give the trans (equatorial)-tert-butyl ether 16 exclusively³⁴ as shown in Scheme I.A.2. The high selectivity is attributed to the large steric requirement of the alkylating agent which is trityl-DMAP salt in this case. Similarly, selective tritylation of primary hydroxyl group over secondary hydroxyl group can be achieved using

Scheme 1-A.1



Scheme 1-A.2



4-dimethylamino-1-triphenylmethyldpyridinium chloride as the alkylating agent.³⁵ The tritylation of the α -methylglucoside can be carried out easily using DMAP as the catalyst.³⁴

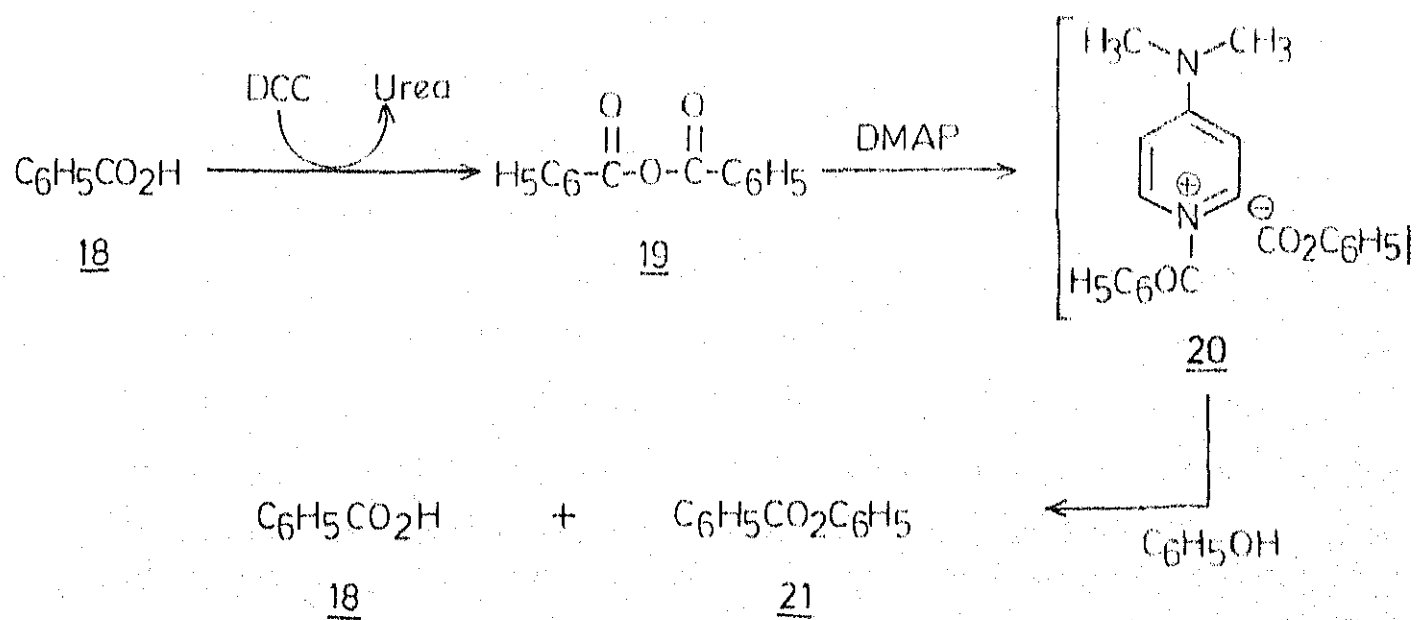
I.A.2.4 Silylation Reactions Catalysed by DMAP

Analogous to the acylation reactions, DMAP has also been efficiently used as a catalyst for the silylation reactions. Thus, a mixture of silyl ether of primary and secondary alcohols is obtained using tert-butyldimethylsilyl chloride.³⁶ Similarly diols react with ditert-butyldichlorosilane in acetonitrile in the presence of DMAP to give ditert-butylsilylene derivatives which are stable towards Lewis acids and hence act as better protecting groups.³⁷

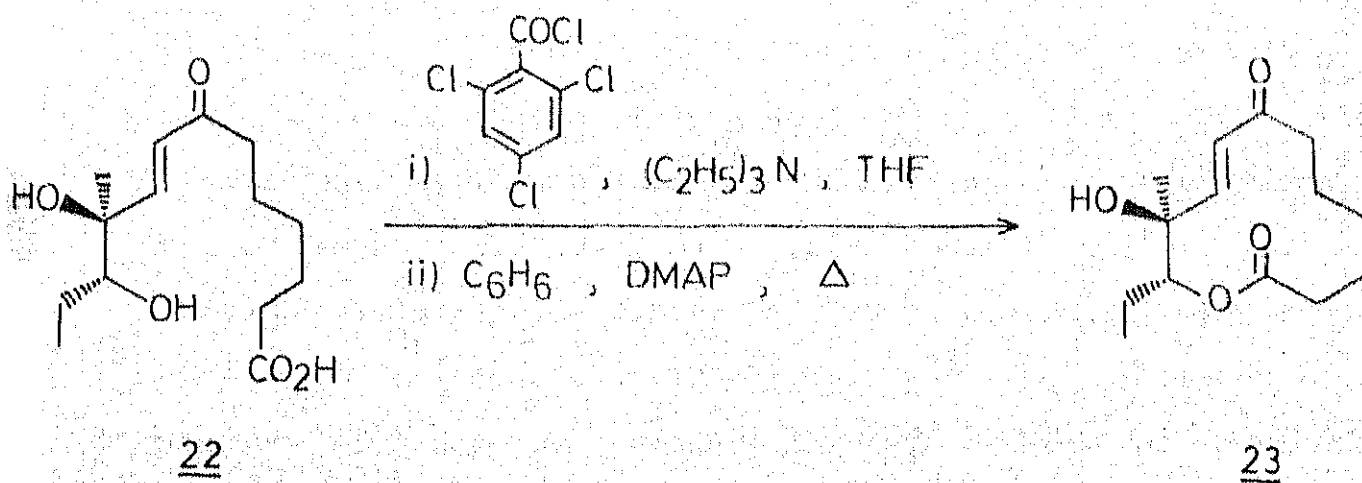
I.A.2.5 Esterifications and Lactonizations Catalysed by DMAP

A superior method for the "exhaustive" esterification of carboxylic acids has emerged from the efforts of several groups of workers.³⁸⁻⁴⁰ For example, esterification of benzoic acid (18) to phenyl benzoate (21) has been achieved successfully in quantitative yield (Scheme I.A.3). This method has merit over the usual dicyclohexylcarbodiimide (DCC) esterification method, in that the preparation of anhydride is not necessary. It also avoids the use of one equivalent of pyridine or triethylamine which results in the diversion of half of the carboxylic acid to byproduct.⁴¹ Alcohols and thiols can be esterified using

Scheme I-A.3



Scheme I-A.4

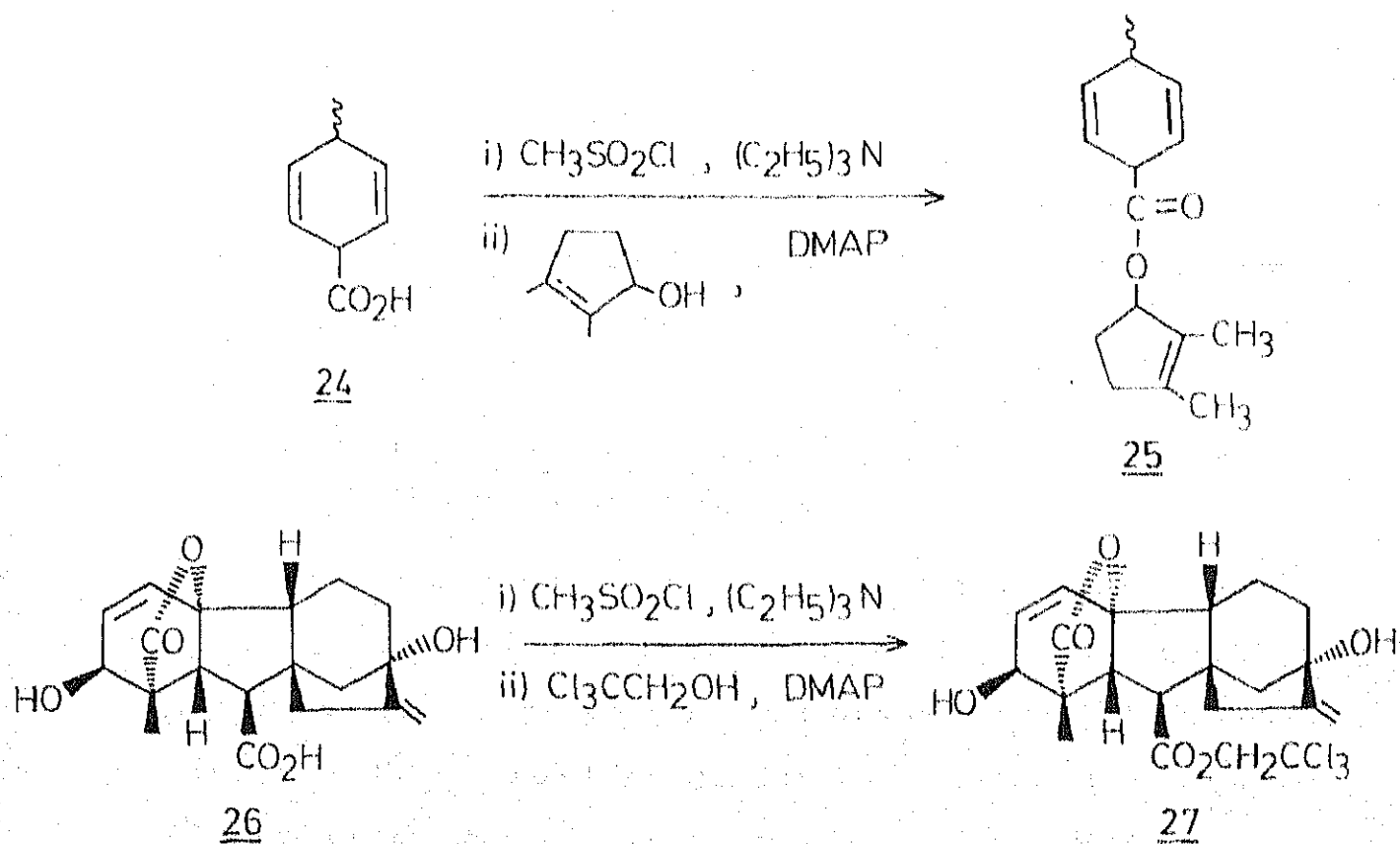


this method.⁴⁰ Thus, thioesters are conveniently prepared by the reaction of acids with thiols and 1-fluoro-2,4,6-trinitrobenzene.⁴² Alternatively, esterification can be achieved through mixed trichlorobenzoic anhydrides and thiols in the presence of DMAP.⁴³ This mixed anhydride approach has provided an excellent method for the preparation of sterically hindered esters and macrocyclic lactones⁴⁴ (Scheme I.A.4). Recently, esterification of carboxylic acids has been carried out under very mild conditions using mixed sulphonic anhydrides of carboxylic acids and various alcohols using DMAP as catalyst (Scheme I.A.5).⁴⁵

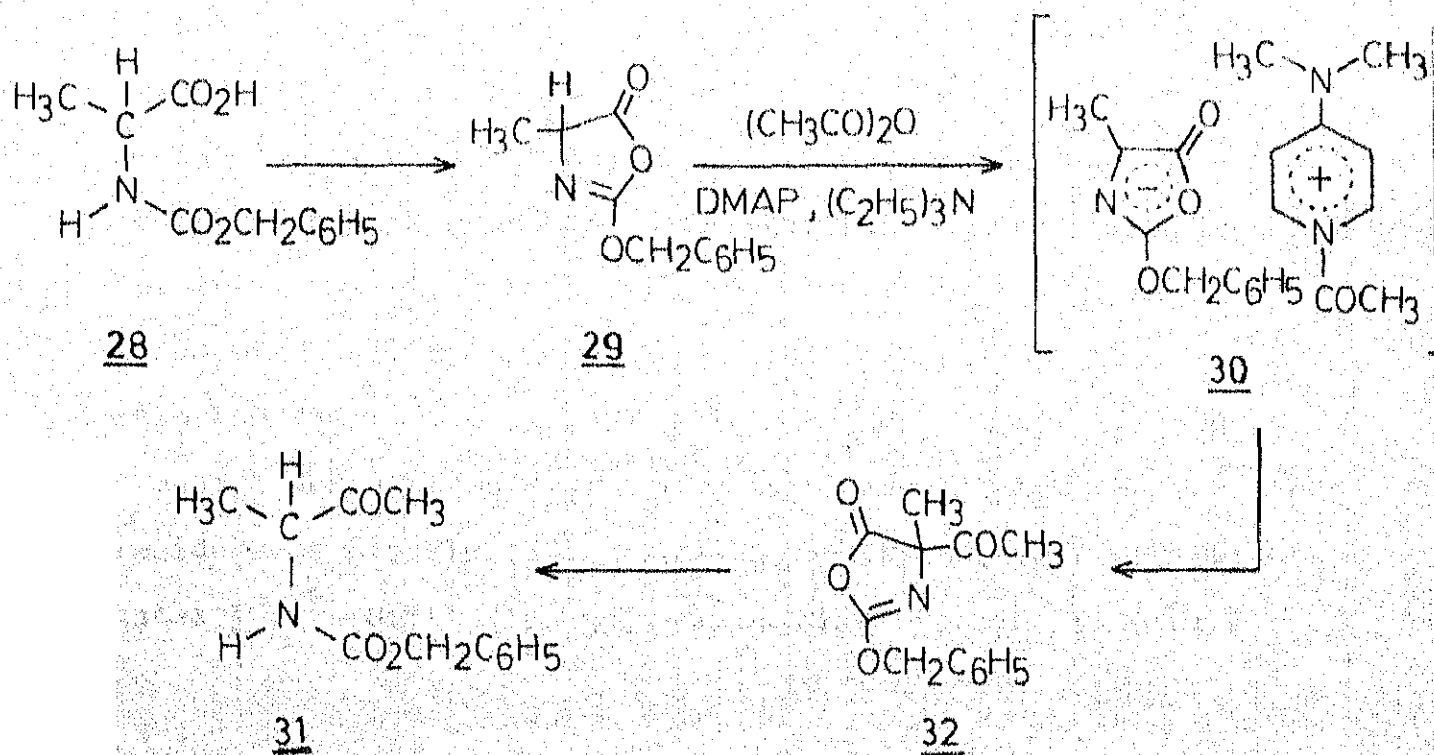
I.A.2.6 Acylation of Enolates

Dimethylaminopyridine catalyses the dimerization of 4-methyl-6-hydroxy-2-pyrone,⁴⁶ thereby offering a new route to the coumarochromanones. The Dakin-West reaction of N-acyl amino acids in which a 2-oxazolin-5-one is acetylated at C-4 position with a carboxylic anhydride can be catalysed by DMAP or DMAP/triethylamine. The reaction proceeds smoothly and with an improved yield (Scheme I.A.6).^{3,47} Similarly, glutamic acid yields a pyrrolidone under Dakin-West reaction conditions in the presence of a catalytic amount of DMAP.⁴⁷ This modification of the Dakin-West reaction has been utilized in the conversion of N-acylamino acids to enamides.⁴⁸ Dimethylaminopyridine also catalyses the rearrangement of 5-acyloxyoxazoles to

Scheme I.A.5



Scheme I.A.6

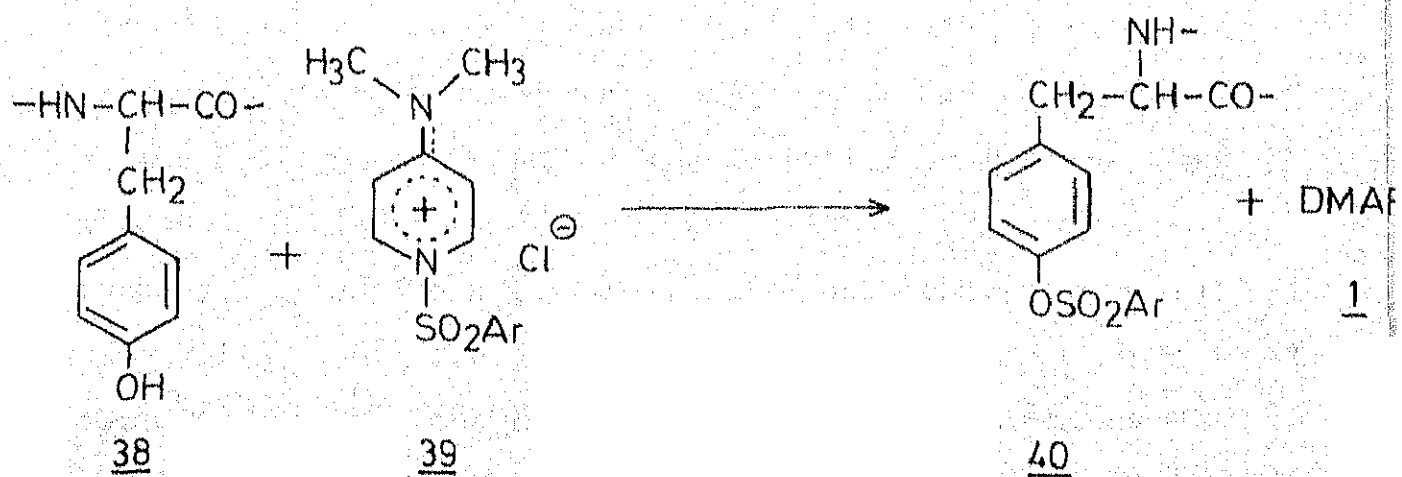
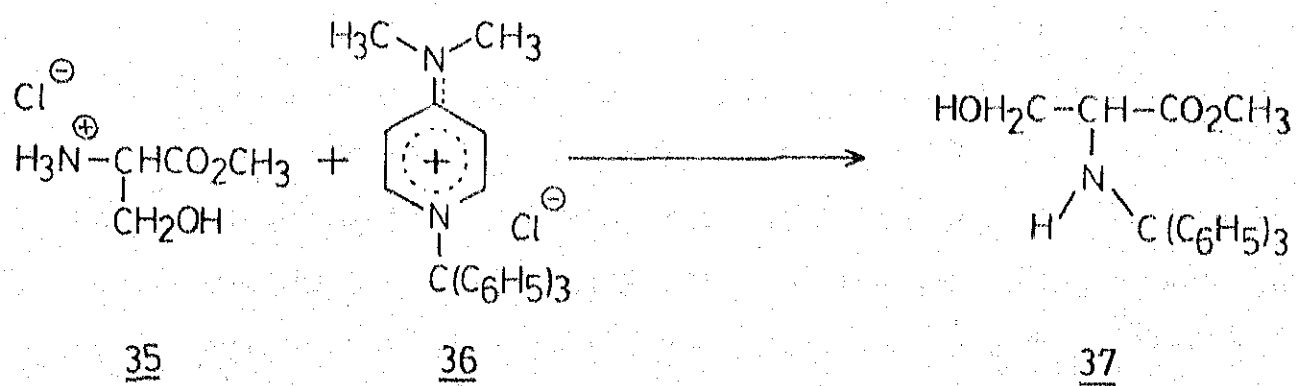
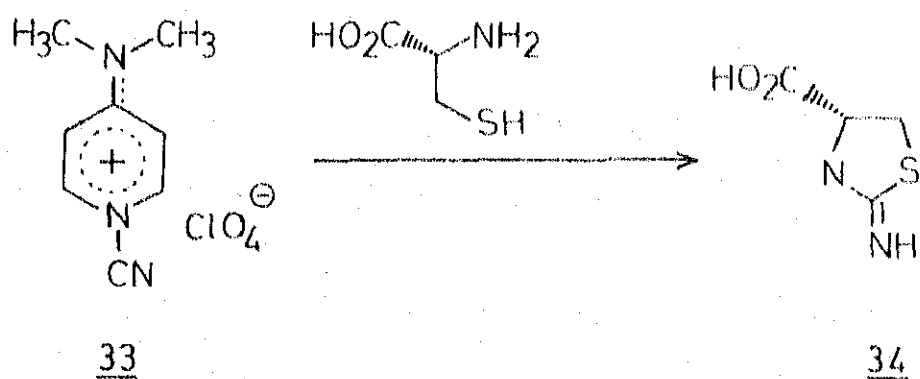


4-acyl-2-oxazolin-5-ones or 2-acyl-3-oxazolin.⁴⁹ This rearrangement has been used as a synthetic tool for the preparation of 3,3,3-trifluoroaniline.⁵⁰ Specific acylations at C-, O- and N- sites have been achieved successfully using DMAP as the catalyst.⁵¹⁻⁵³

I.A.2.7 4-Dimethylaminopyridinium Salts as Reagents for Functional Group Transfer

Dimethylaminopyridine forms stable salts with several compounds which serve as interesting reagents for the transfer of various functional groups. Wakselman and Guibe'-Jampel have shown that 1-tert-butoxycarbonyl-4-dimethylaminopyridinium chloride or fluoborate can be used for the transfer of butoxycarbonyl groups to amines and amino acids.^{54,55} Similarly the reaction of 1-cyano-4-dimethylaminopyridinium perchlorate (33) with cysteine gives rise to 2-iminothiazolidine-4-carboxylic acid (34) in quantitative yield⁵⁶ as outlined in Scheme I.A.7. Similarly, transfer of phosphono group to amines has been achieved using N-phosphono-4-dimethylaminopyridinium salts.^{57,58} Selective N-tritylation of serine methyl ester (35) has been accomplished by the use of N-trityldimethylaminopyridinium chloride (36).³⁵ Other salts of DMAP such as N-tosyl and N-dansyl derivatives (39), react selectively with the tyrosine residues of proteins 38 in aqueous media to give O-arylsulphonates 40.⁵⁹ Similarly, tert-butoxydimethylaminopyridinium

Scheme IA 7



chloride has been used for N-blocking in amino acids such as glycine, glutamic acid, serine, lysine, ethyl glutamate etc.⁶⁰

DMAP is nowadays commonly employed as a catalyst in the solid phase peptide syntheses also.⁶¹⁻⁶³

I.A.2.8 Mechanism of Acylation Reactions with DMAP

It has been suggested that the acylation reactions using DMAP catalysis proceed through the intermediacy of 1-acetyl-4-dimethylaminopyridinium acetate (41). Höfle has cited evidence for the presence of such an ion pair in solution by PMR studies.¹ Based on these investigations, a mechanism for the acylation has been proposed, involving the initial attack of the highly nucleophilic dimethylaminopyridine on the acylating agent, such as acetic anhydride to form the 1-acetyl-4-dimethylaminopyridinium acetate (41) (nucleophilic catalysis) as outlined in Scheme I.A.8. Because of the charge delocalization, 41 will be present as loosely bound ion pair, thus facilitating the attack of the nucleophile (R-OH) on the activated acyl group. The neighbouring acetate anion causes an increase in the reaction rate by abstracting a proton from the nucleophile (general base catalysis). This mechanism also explains the superiority of the carboxylic anhydrides for acylations over the corresponding acyl chlorides, wherein the ions are tightly bound and the chloride ion is not that basic.

An alternatively suggested mechanism⁶⁴ is that 41 is not an intermediate but might be forming in a by-pass to the main mechanistic pathway. During the studies on the acetylation of tert-butanol Jampel et al.⁶⁴ proposed a mechanism which involves the rate determining nucleophilic attack of DMAP on a acetic anhydride-tert-butanol complex 45 formed in a pre-equilibrium, giving rise to an ion pair solvated by tert-butanol as depicted in Scheme I.A.9. Then this alcohol which is in the close vicinity reacts rapidly with the carbonyl of the acetyl pyridinium ion to give the tert-butyl acetate (46).

From a brief review of the literature on dimethylamino-pyridine catalysed reactions, it was found that the reactions of 1,2-ditertiary diols at higher concentration of dimethylaminopyridine-acetic anhydride have not been studied. This would be particularly interesting since there is an early report of the formation of acetoacetates during the attempted acylation of 17- α -hydroxysteroids with excess of acetic anhydride and DMAP in pyridine.¹ This observation prompted us to study in detail the mode of reaction of pinacols under similar conditions employing higher concentration of 4-dimethylaminopyridine and acetic anhydride.

I.A.3 RESULTS AND DISCUSSION

The objective of the present investigation has been to study the reaction of 1,2-ditertiary diols with the versatile acylation reagent, acetic anhydride and 4-dimethylaminopyridine at high concentrations. With a view to examining the behaviour of pinacols under such reaction conditions, we treated the representative substrate, 2,3-dihydroxy-2,3-dimethylbutane (48) with DMAP (1 equivalent) and acetic anhydride (2.2 equivalents) at ca. 85 °C for 3 h. A colourless crystalline compound 49 was isolated as the major product (51%), m.p. 179-180 °C. The IR spectrum of the compound 49 showed a strong absorption at 1790 cm^{-1} characteristic of a five membered cyclic carbonate. The PMR spectrum of 49 showed a sharp singlet at δ 1.3 which can be assigned to the methyl group protons (Fig. I.A.1). The mass spectrum showed a molecular ion peak at m/e 144. Interestingly all these data fit in very well with the structure of the cyclic carbonate, 2-oxo-4,4,5,5-tetramethyl-1,3-dioxolane (49).⁶⁵ The other products isolated in the reaction were 2-acetoxy-3-hydroxy-2,3-dimethylbutane (50, 26%), and 2,3-diacetoxy-2,3-dimethylbutane (51, 17%), m.p. 64-65 °C (lit.⁶⁶ m.p. 65°C), along with a small amount of unchanged starting material 48 (Scheme I.A.10). Acetone was also found to be formed as a byproduct in the reaction (2,4-dinitrophenylhydrazone, m.p. 127-128°C⁶⁵). The IR spectrum of the monoacetate 50 showed absorptions at 3470 cm^{-1} characteristic of a hydroxyl group and at 1735 cm^{-1} corresponding

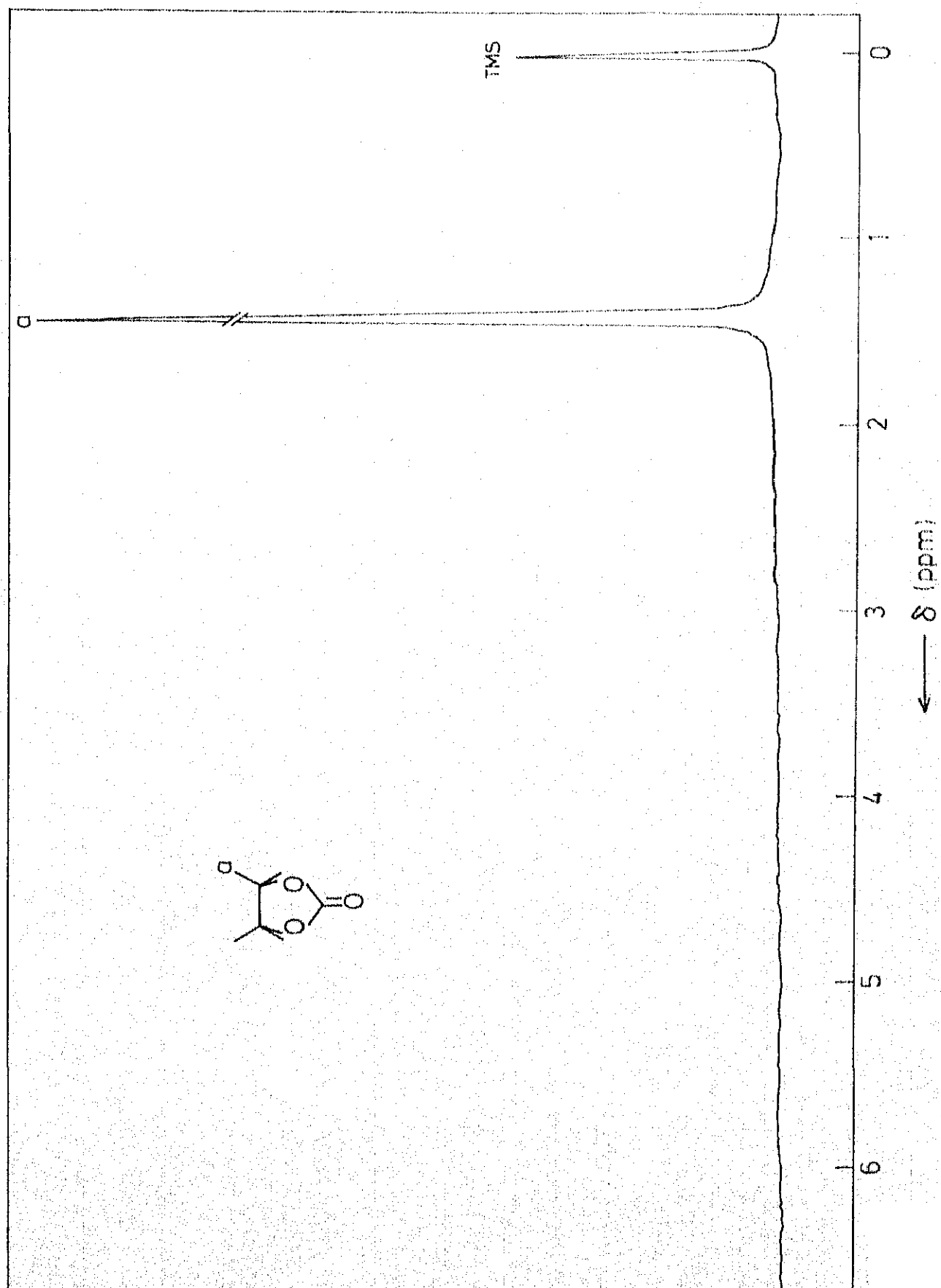
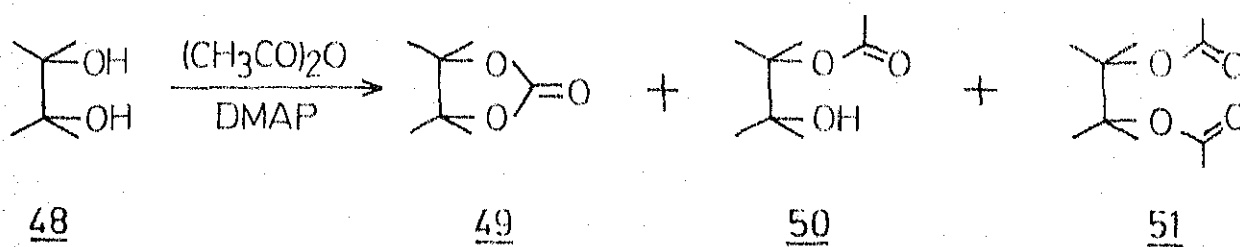
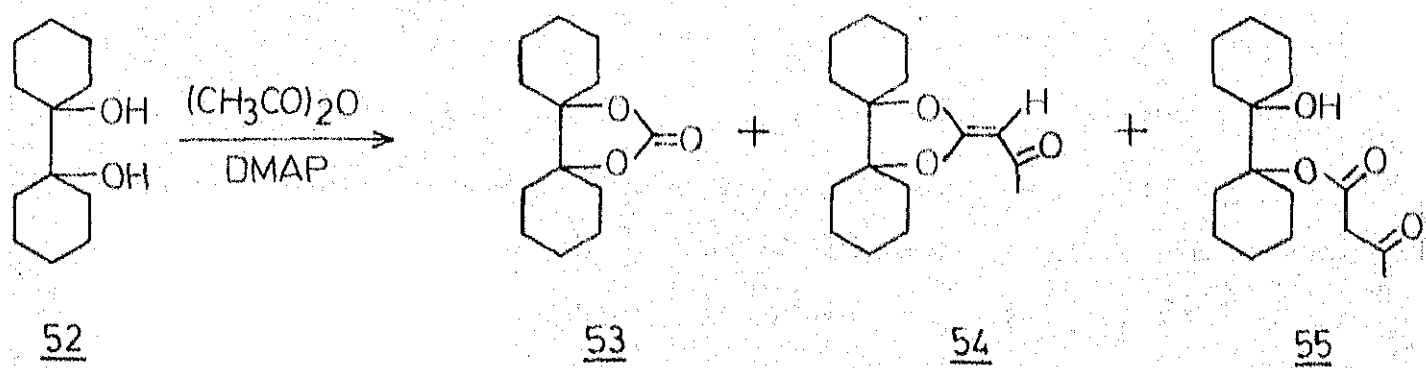


Fig. I-A-1 ^1H NMR spectrum (100 MHz) of 49.

Scheme I-A-10



Scheme I-A-11



to an ester carbonyl group. The PMR spectrum showed two singlets at δ 1.3 (6H) and 1.4 (6H) for the two sets of gem-dimethyl groups and another singlet at δ 1.95 (3H) corresponding to the methyl protons of the acetate group. The hydroxyl proton appeared at δ 3.26 (1H) which was D₂O exchangeable. The mass spectrum showed a peak at m/e 145 ($M^+ - CH_3$). The IR spectrum of the diacetate 51 showed a strong ester carbonyl absorption at 1730 cm^{-1} . The PMR spectrum of 51 indicated the presence of two singlets at δ 1.3 (12H) and 2.0 (6H) assigned to the methyl protons.

In order to examine the generality of the above reaction, 1,2-ditertiary diols such as 1,1'-dihydroxybicyclohexane (52) and 1,1'-dihydroxybicyclopentane (61) have been studied. These substrates were prepared by the reductive coupling of the corresponding carbonyl compounds, employing low-valent titanium species.⁶⁷

Treatment of pinacol 52 with 4-dimethylaminopyridine (1, 1 equivalent) and acetic anhydride (2.2 equivalents) at ca. 85 °C for 4 h, gave a mixture of products (Scheme I.A.11). The crude product was chromatographed over silica gel. Elution of the column with ether-petroleum ether (1:9) gave a 15% yield of 2-acetonylidene-4,5-bis(cyclohexyl)-1,3-dioxolane (54), a 21% yield of 2-oxo-4,5-bis(cyclohexyl)-1,3-dioxolane (53), m.p. 178-179 °C, a 17% yield of 1-acetoacetyloxy-1'-hydroxy-1,1'-bicyclohexane (55), along with the recovered starting material 52. The α,β -unsaturated ketone 54 showed strong fluorescence under the

UV light source. The IR spectrum showed a strong absorption at 1680 cm^{-1} characteristic of a conjugated carbonyl group and at 1640 cm^{-1} indicating the presence of a double bond of an enol ether. The PMR spectrum showed a multiplet centred at $\delta 1.5$ (20 H) due to the methylene protons. In addition, a singlet at $\delta 2.26$ (3H) assigned to the methyl protons and yet another singlet at 4.8 (1H) appeared in the spectrum due to the vinylic proton (Fig. I.A.2). The mass spectrum showed a molecular ion peak at m/e 264. Some of the important fragmentation modes of the molecular ion have been shown in Scheme I.A.12. The compound 53 gave a strong IR absorption at 1780 cm^{-1} characteristic of a cyclic carbonate. The PMR spectrum of 53 showed a multiplet centred at $\delta 1.6$ due to the methylene protons (Fig. I.A.3). The mass spectrum indicated a molecular ion peak at m/e 224 and a peak at m/e 180 ($M^+ - 44$) arising from the loss of carbon dioxide characteristic of the cyclic carbonates. Some of the prominent fragmentation modes have been given in Scheme I.A.13. The compound 55 had strong IR absorptions at 3440 cm^{-1} characteristic of the hydroxyl groups and at 1730 and 1700 cm^{-1} corresponding to the ester and the keto groups, respectively. The PMR spectrum gave a multiplet centred at $\delta 1.49$ (20 H) due to the methylene protons, a singlet at 2.25 (3H) assigned to the methyl protons and another singlet at 3.5 (2H) corresponding to the methylene protons. The hydroxyl protons appeared at $\delta 4.18$ (1H, D_2O exchangeable), (Fig. I.A.4).

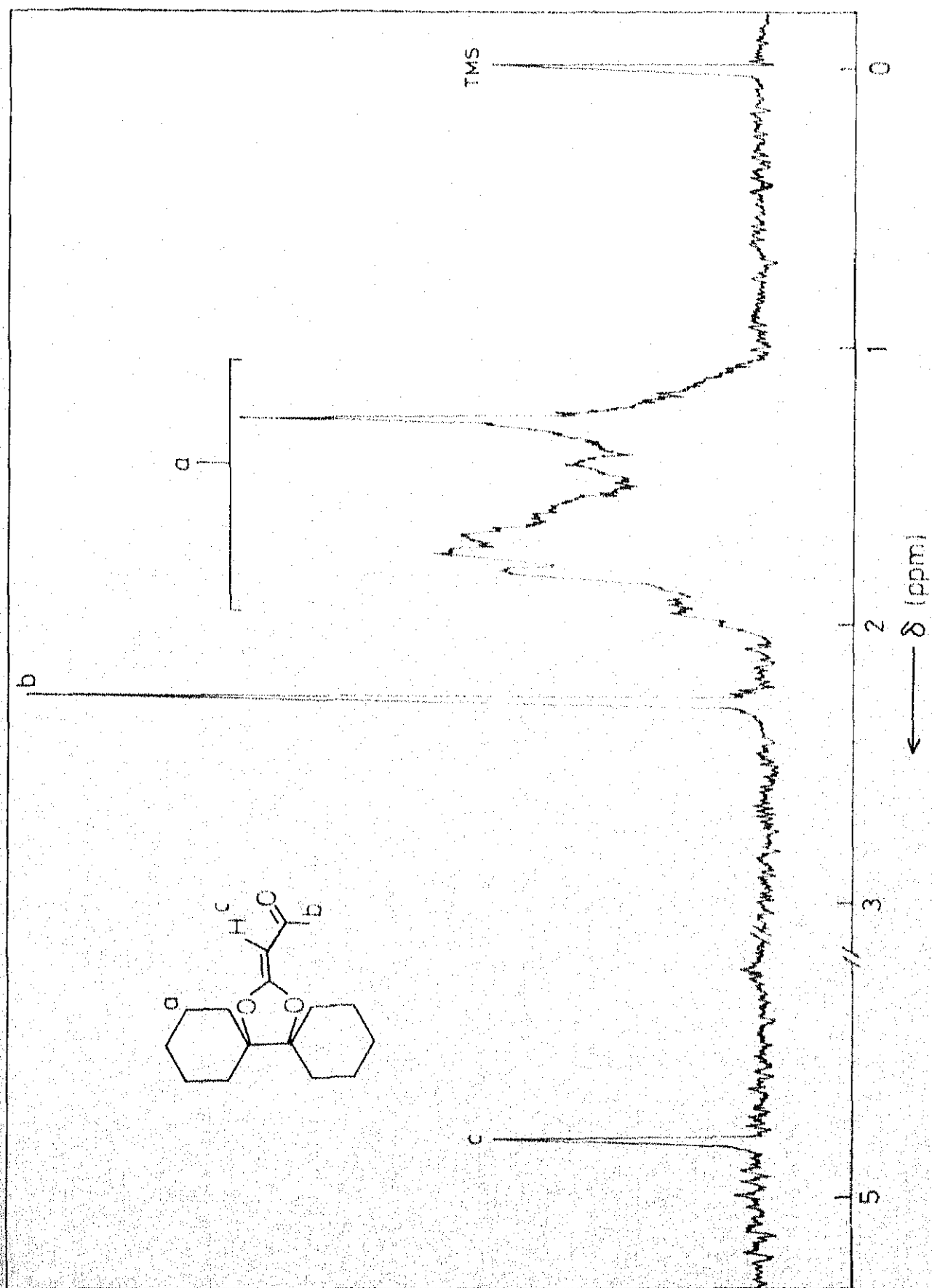
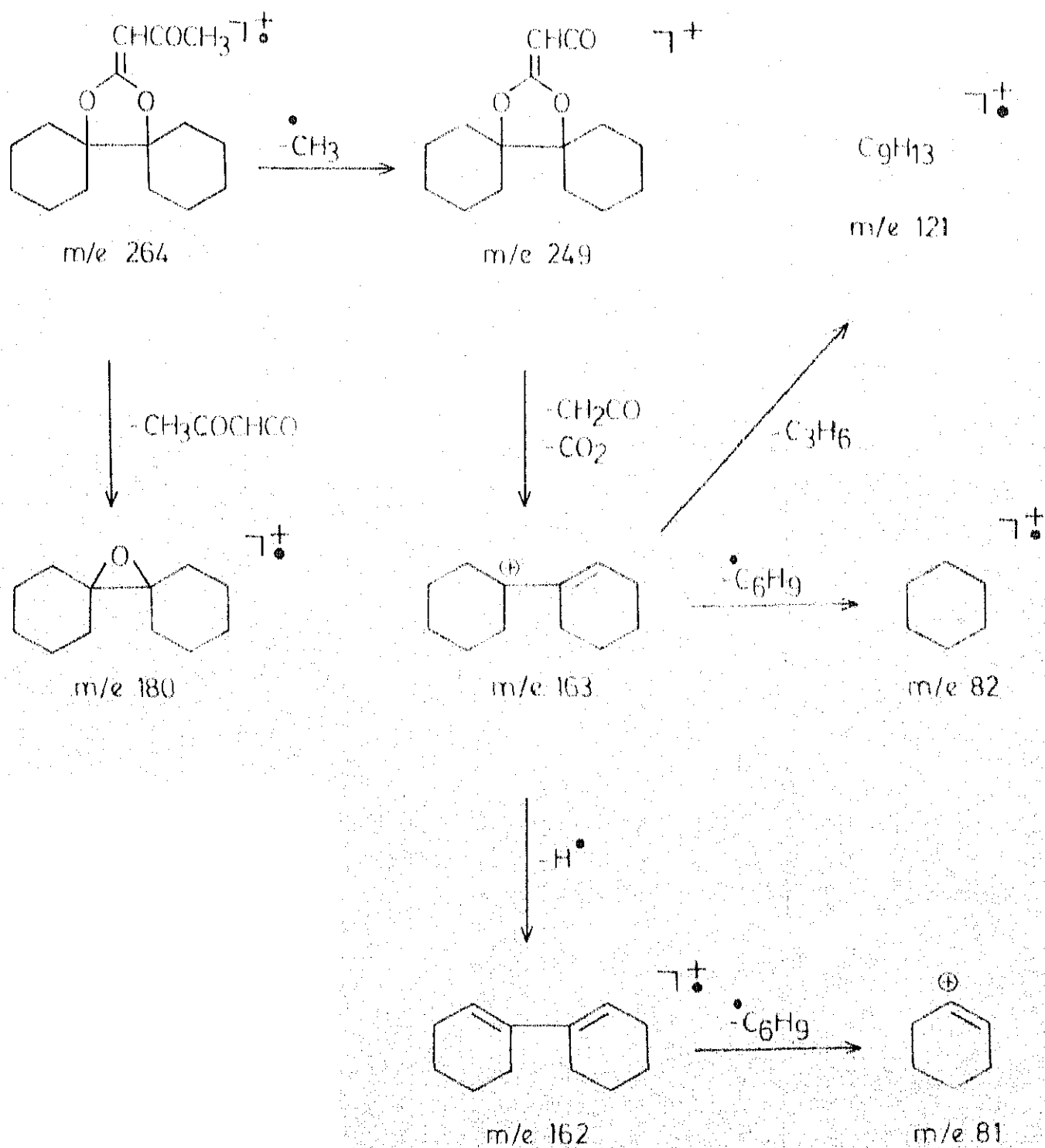


Fig. I.A.2 ^1H NMR spectrum (100 MHz) of **54**.

Scheme I-A-12



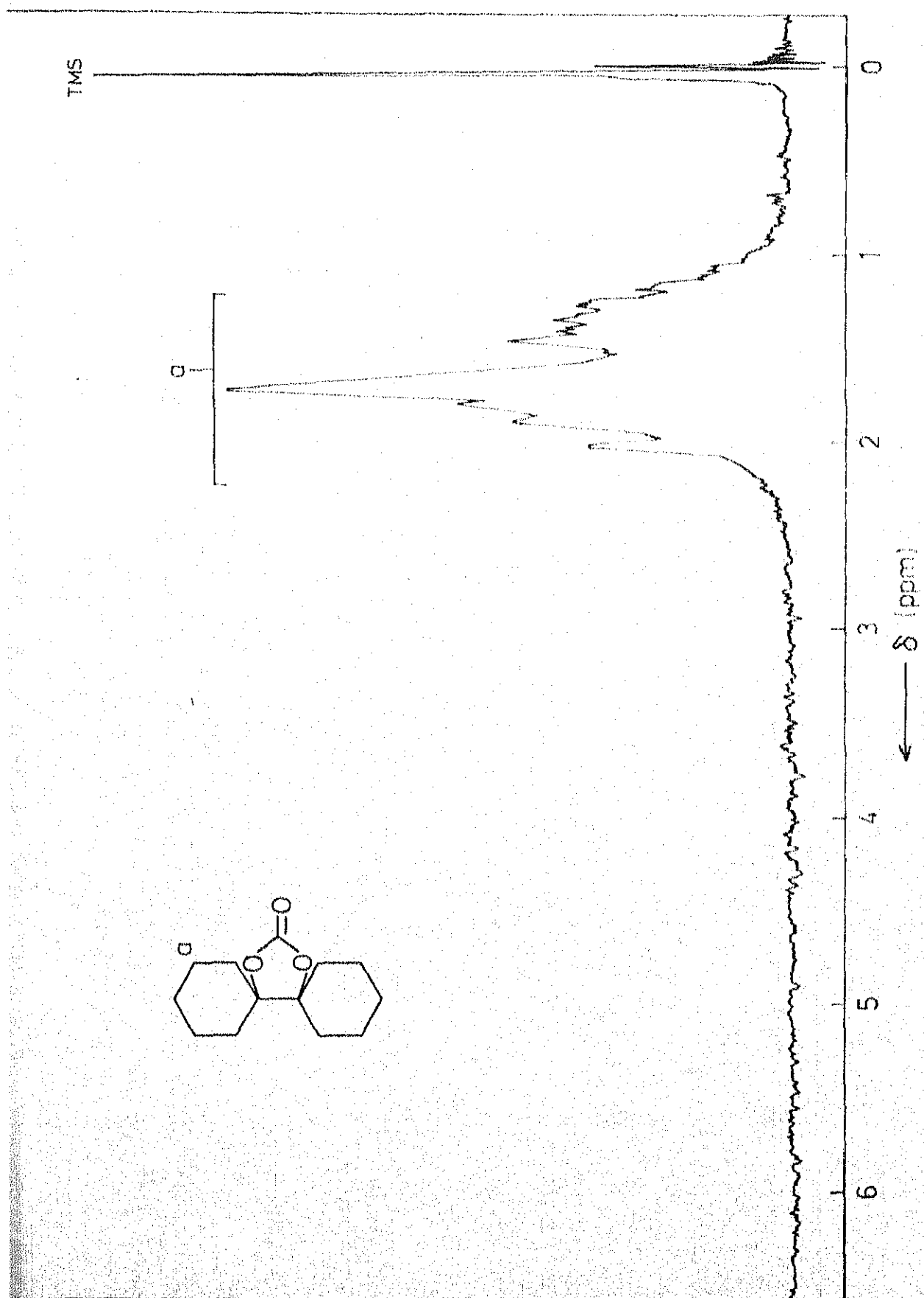
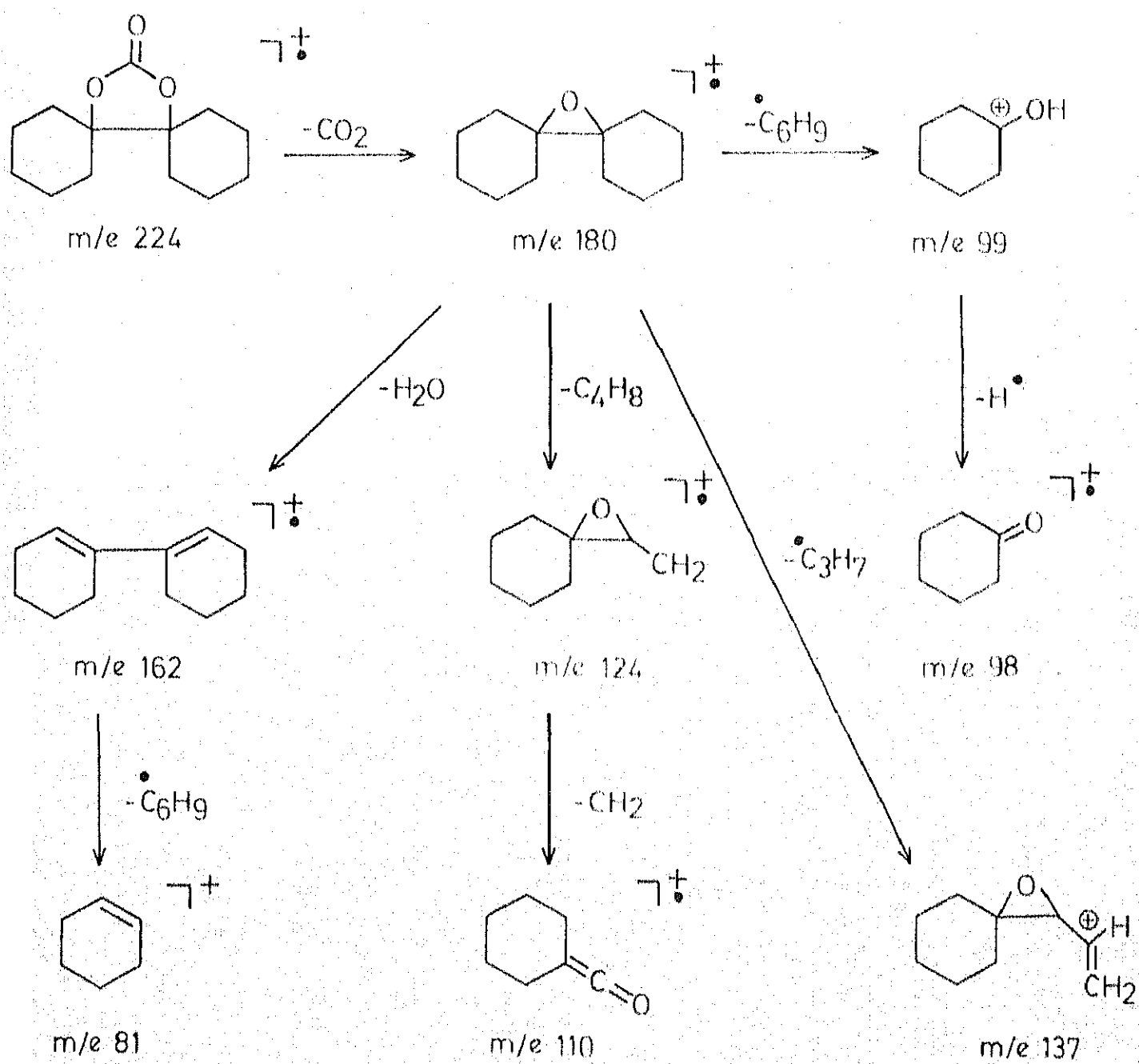


Fig. I-A-3 ^1H NMR spectrum (100 MHz) of **53**.

Scheme I-A.13



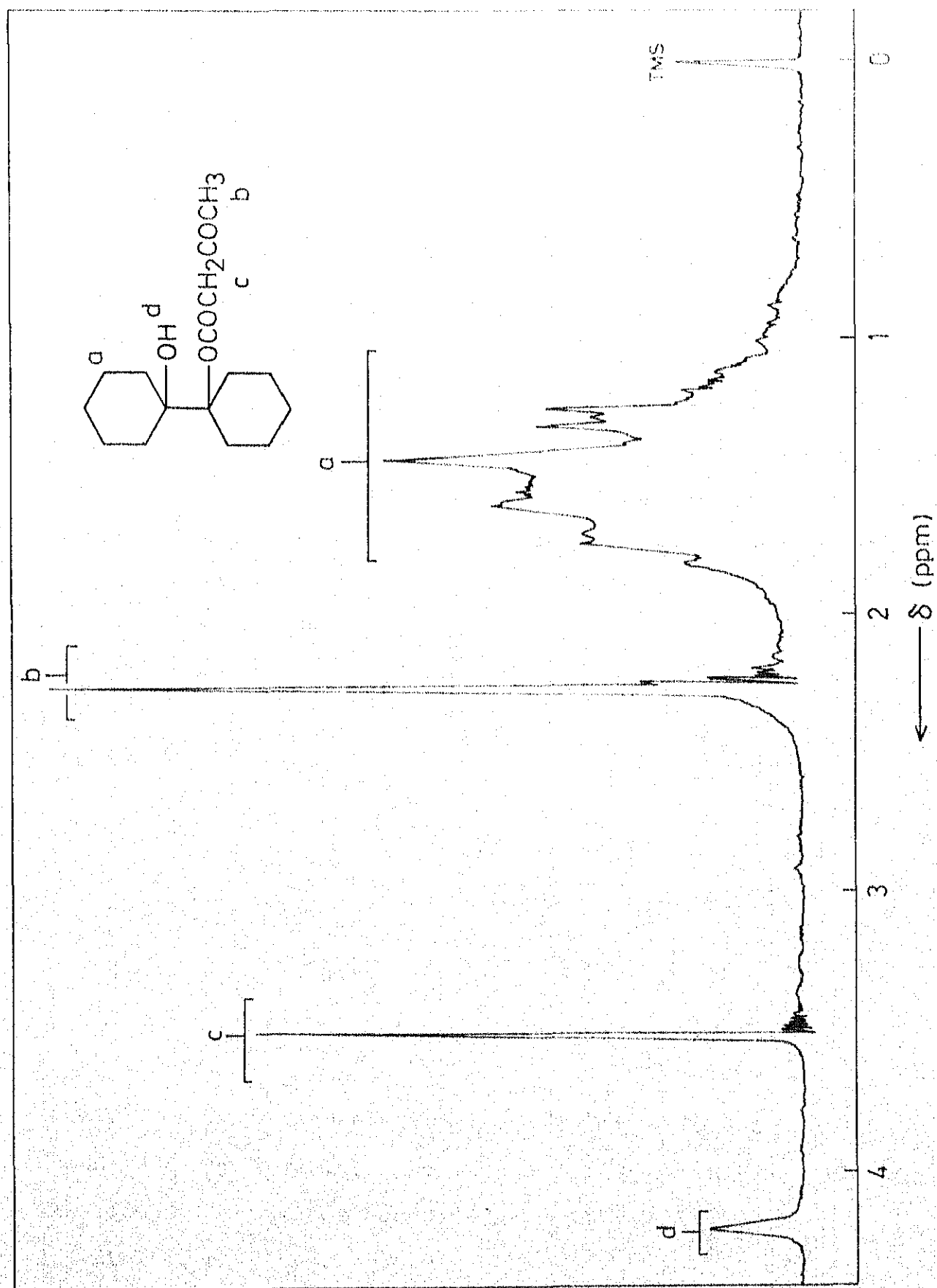
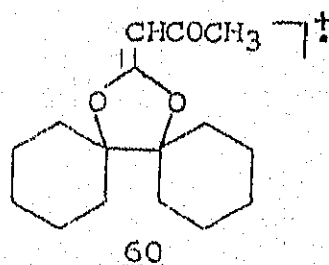
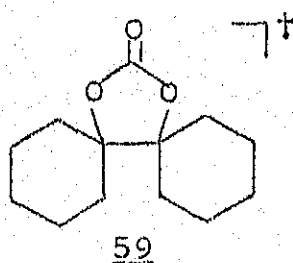
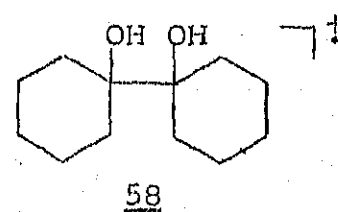
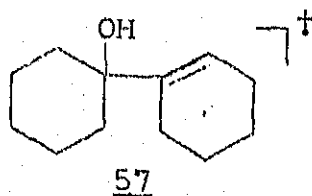
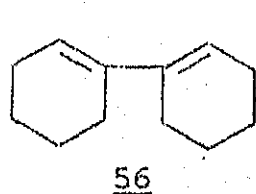


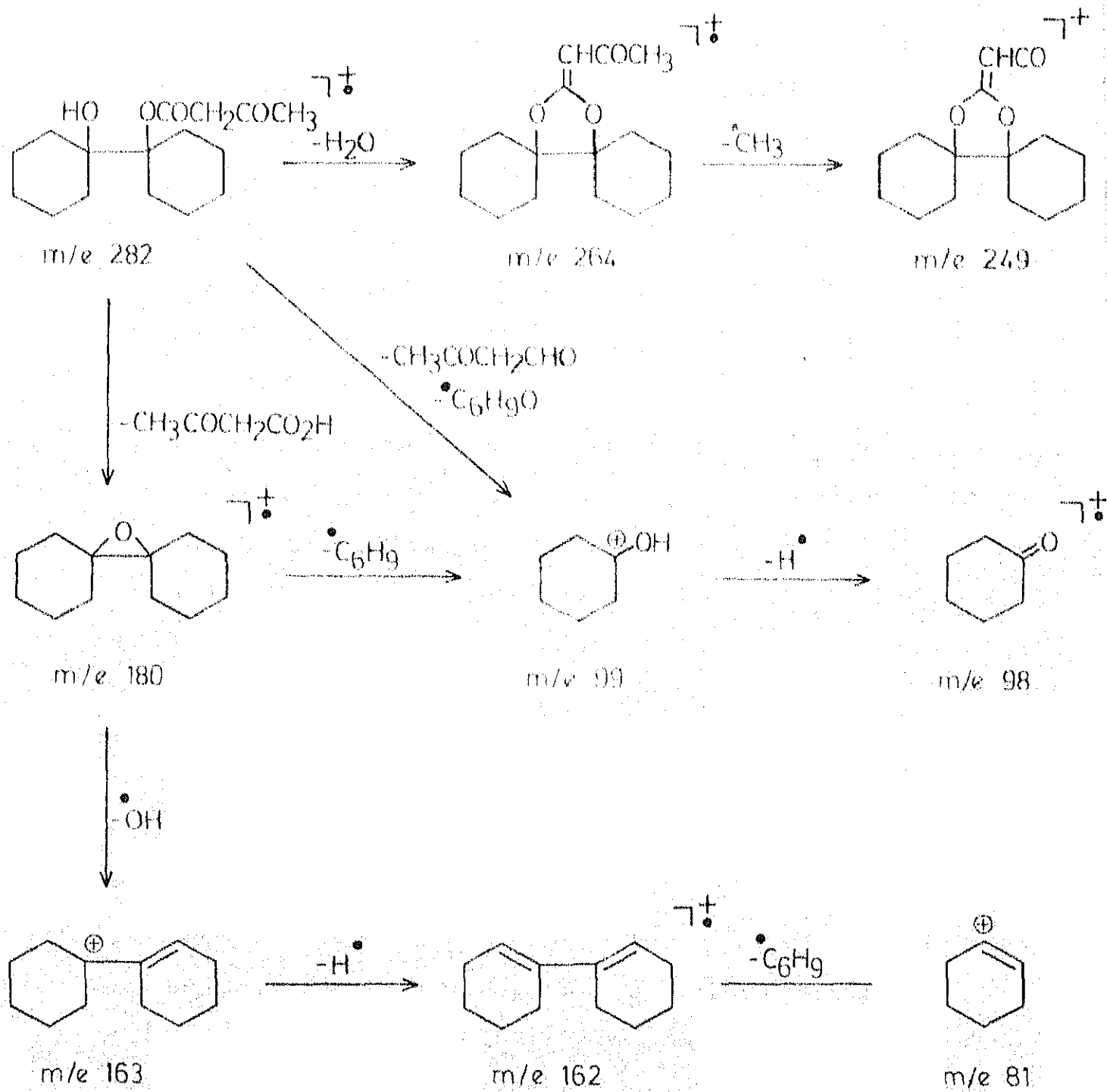
Fig. IA-4 ^1H NMR spectrum (100 MHz) of 55.

The monoacetoacetate 55 was thermally labile and when a gas chromatographic analysis on a SE-30 column at 120°C was attempted, it seemed to decompose giving rise to five different components. A GC-MS analysis gave positive evidence to the structure of the components being formed and indicated the presence of 1,1'-bicyclohexene (56, $M^+ = 162$), 1-hydroxycyclohexyl-1'-cyclohexene (57, $M^+ = 180$), 1,1'-dihydroxybicyclohexane (58, $M^+ = 198$), 2-oxo-4,5-bis(cyclohexyl)-2,3-dioxolane (59, $M^+ - 44 = 180$) and 2-acetonylidene-1,5-bis(cyclohexyl)-1,3-dioxolane (60, $M^+ = 264$). The mass spectrum of 55 showed a peak at m/e 264



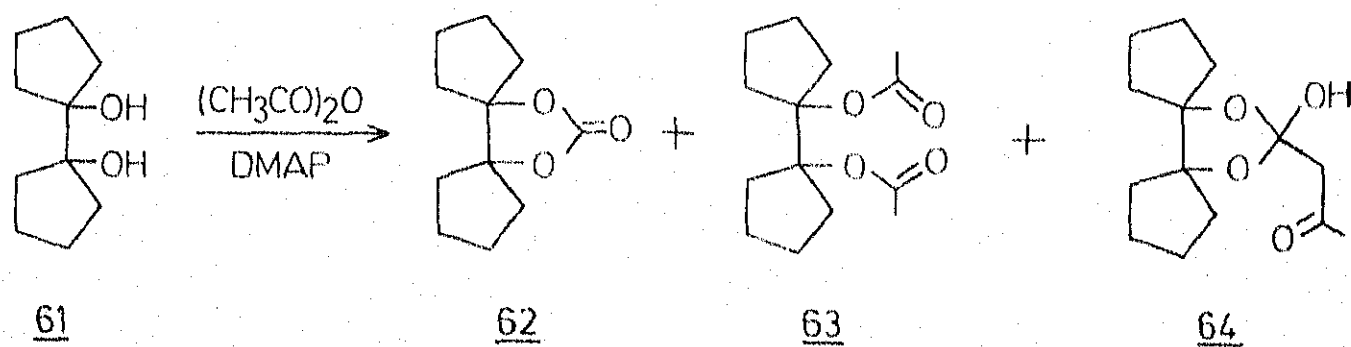
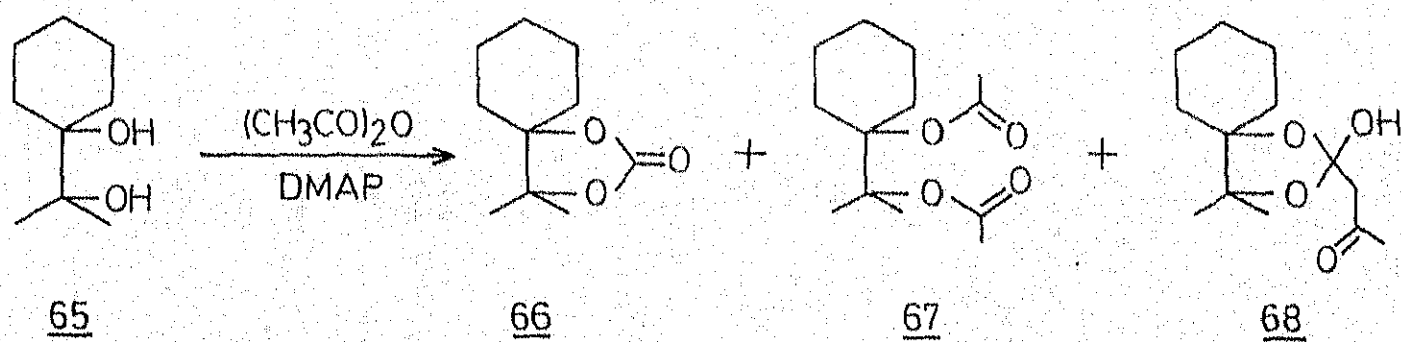
($M^+ - 18$). Other fragmentation modes of the molecular ion are shown in Scheme I.A.14. The reaction of 52 with Ac_2O /DMAP was also found to give acetone as a byproduct (characterised as the 2,4-dinitrophenylhydrazone).

Scheme I.A.14



On the other hand, treatment of 1,1'-dihydroxybicyclopentane (61) with 4-dimethylaminopyridine and acetic anhydride under analogous conditions gave a brown liquid which upon flash chromatography yielded 24% of 2-oxo-4,5-bis(cyclopentyl)-1,3-dioxolane (62), m.p. 89-90°C, 32% of 1,1'-diacetoxy-1,1'-bicyclopentane (63), 16% of 2-acetonyl-2-hydroxy-4,5-bis(cyclopentyl)-1,3-dioxolane (64) and a small amount of unchanged pinacol 61 (Scheme I.A.15). Acetone was also found to form in this reaction.

The IR spectrum of the cyclic carbonate 62 showed a strong absorption at 1780 cm^{-1} characteristic of the cyclic carbonate. The PMR spectrum indicated the presence of a multiplet centred at $\delta 1.9$ due to the methylene protons (Fig. I.A.5). The mass spectrum gave a molecular ion peak at m/e 196 and a peak at m/e 152 ($M^+ - 44$) due to the loss of carbon dioxide, characteristic of the cyclic carbonates. The diacetate 63 showed an absorption at 1730 cm^{-1} in the IR spectrum, typical of the ester carbonyl group. The PMR spectrum of 63 showed a multiplet centred at $\delta 1.62$ (16H), assigned to the methylene protons and a sharp singlet at 2.04 (6H) corresponding to the methyl group protons. The monoacetoacetate 64 indicated two carbonyl absorptions in the IR spectrum at 1705 and 1735 cm^{-1} characteristic of keto and ester functionalities respectively. The hydroxyl group absorption appeared at 3415 cm^{-1} . The PMR spectrum of 64 showed a multiplet centred at $\delta 1.7$ (16H) due to the methylene protons.

Scheme I-A-15Scheme I-A-16

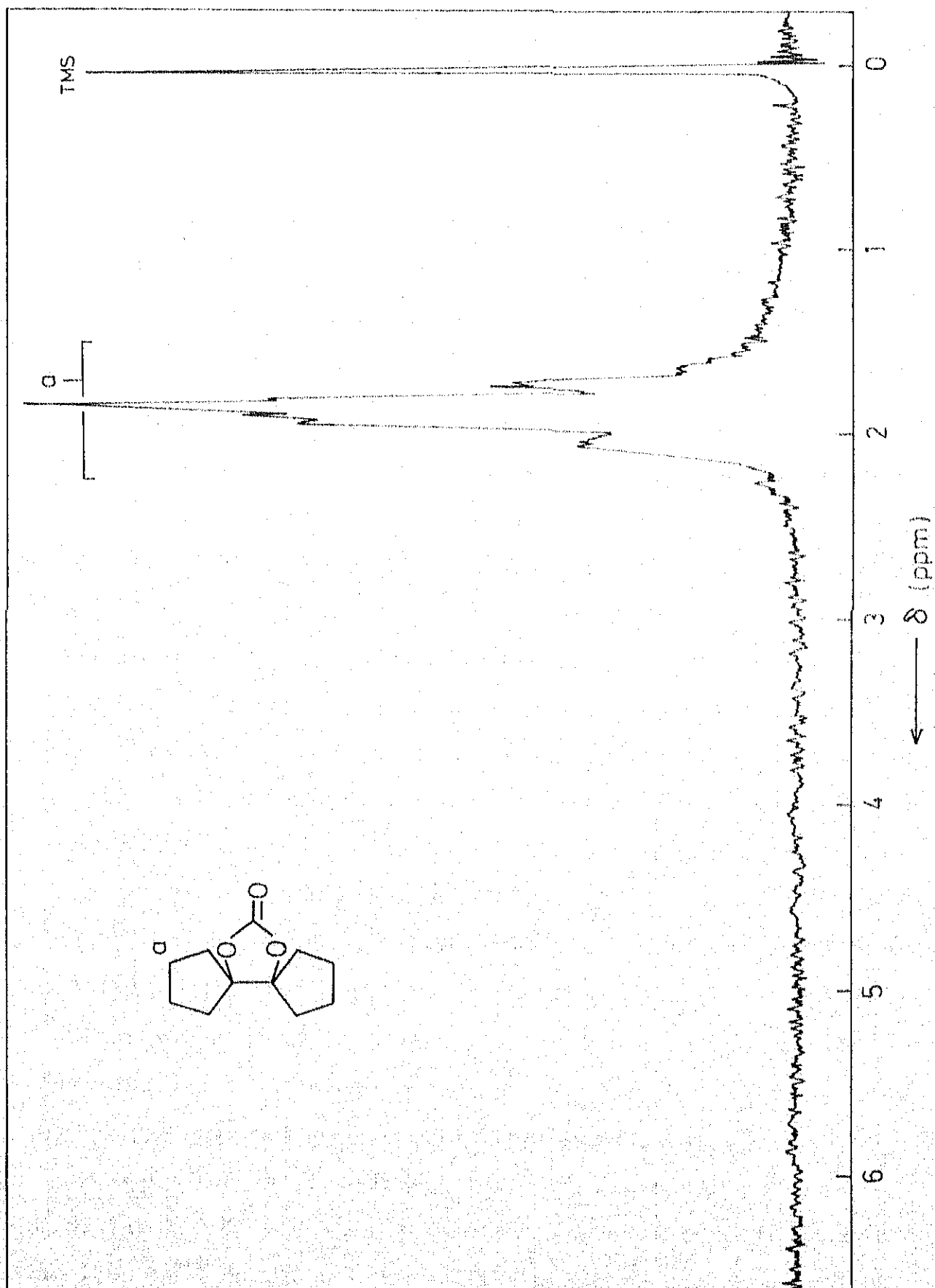


Fig. I-A-5 ^1H NMR spectrum (100 MHz) of 61.

The methyl and the methylene protons appeared together as a singlet at 2.08 (5H). The spectrum also showed a singlet at 4.33 (1H) due to the hydroxyl group proton (D_2O exchangeable) (Fig. I.A.6). The mass spectrum showed a molecular ion peak at m/e 254. The monoacetoacetate 64 on standing for a long time or on warming, resulted in the formation of the carbonate 62.

The similarity in the behaviour of the symmetrical pinacols 48, 52 and 61 towards acetic anhydride and 4-dimethylaminopyridine, prompted us to examine the behaviour of an unsymmetrical pinacol, 1-(2'-hydroxypropyl)cyclohexanol (65) under analogous conditions. As expected, the reaction of 65 with acetic anhydride and DMAP also gave a mixture of products which was purified by flash chromatography (Scheme I.A.16). Elution of the column with ether-petroleum ether (1:19) gave a 17% yield of 1-(2'-acetoxypropyl)cyclohexyl acetate (67) which showed a strong IR absorption at 1735 cm^{-1} characteristic of the ester carbonyl group. The PMR spectrum showed a singlet at δ 1.09 (6H) due to the gem-dimethyl group protons, a multiplet centred at 1.3 (10 H) due to the methylene protons and a singlet at 1.53 (6H) assigned to the methyl protons of the acetate moieties. The mass spectrum showed a peak at m/e 182 ($M^+ - CH_3COOH$). Further elution of the column with ether-petroleum ether (1:9) afforded 2-oxo-4-cyclohexyl-5,5-dimethyl-1,3-dioxolane (66, 34%), m.p. 112-112.5°C. The IR spectrum showed a strong absorption at 1780 cm^{-1} characteristic of the carbonyl group of cyclic

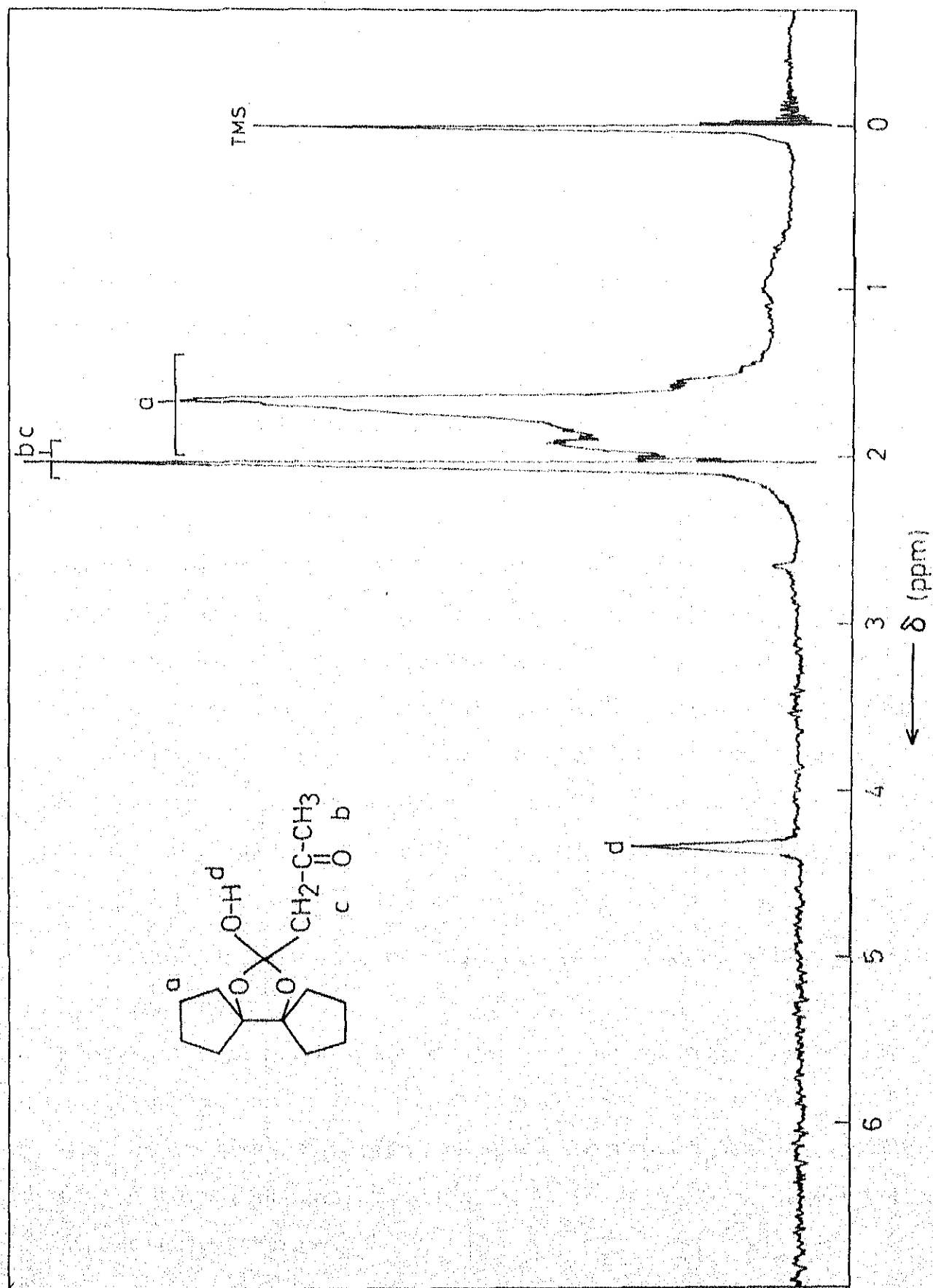


Fig. I-A-6 ^1H NMR spectrum (60 MHz) of 64.

carbonate. The PMR spectrum showed a singlet at $\delta 1.36$ (6H) assigned to the protons of the gem-dimethyl group and a broad multiplet centred at 1.74 (10 H) due to the methylene protons (Fig. I.A.7). The mass spectrum indicated a molecular ion peak at m/e 184 and a peak at m/e 140 ($M^+ - 44$) which is arising due to the loss of carbon dioxide. Continued elution of the column with ether-petroleum ether (1:9) gave a 28% yield of 2-acetyl-2-hydroxy-4-cyclohexyl-5,5-dimethyl-1,3-dioxolane (68). The compound 68 showed the IR absorptions at 3440 cm^{-1} due to the hydroxyl group and at 1735 and 1710 cm^{-1} characteristic of the ester and the ketone functionalities, respectively. The PMR spectrum showed a multiplet centred at $\delta 1.4$ (10 H) due to the methylene protons, a singlet at 1.53 (6H) assigned to the gem-dimethyl groups, a singlet at 2.01 (3H) corresponding to the methyl protons and a singlet at 2.23 (2H) corresponding to the methylene protons. The hydroxyl group proton indicated a singlet at $\delta 2.92$ (1H) which was D_2O exchangeable (Fig. I.A.8).

In all the cases of 1,2-ditertiary alcohols studied, it has been observed that apart from a small amount of normal acetylation products, the cyclic carbonates and the monoacetoacetates are the major reaction products. The formation of acetone in these reactions should also be noted. The formation of the rather unusual product, the cyclic carbonate, needed a mechanistic probing.

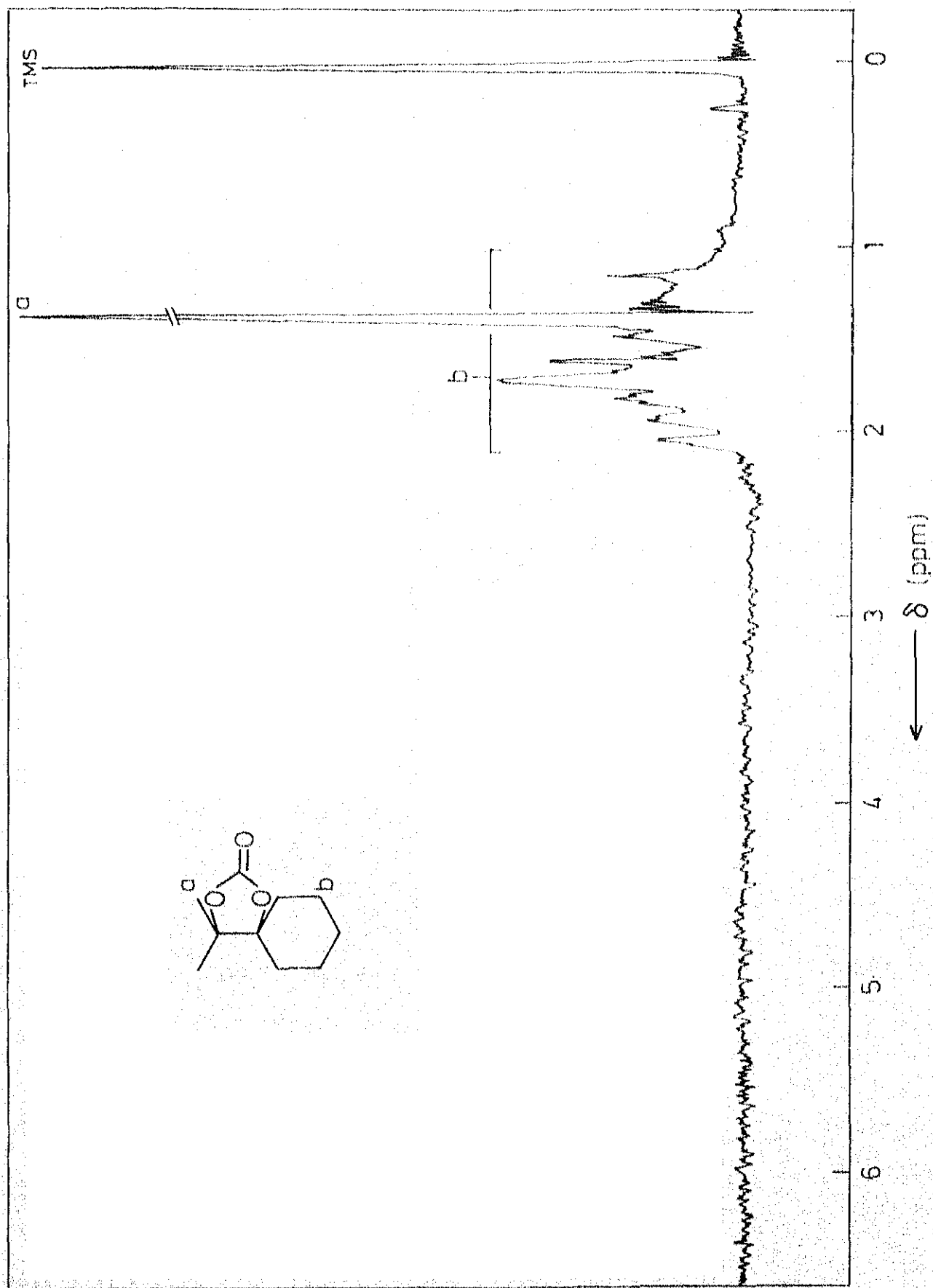


Fig. I-A-7 ^1H NMR spectrum (100 MHz) of 66.

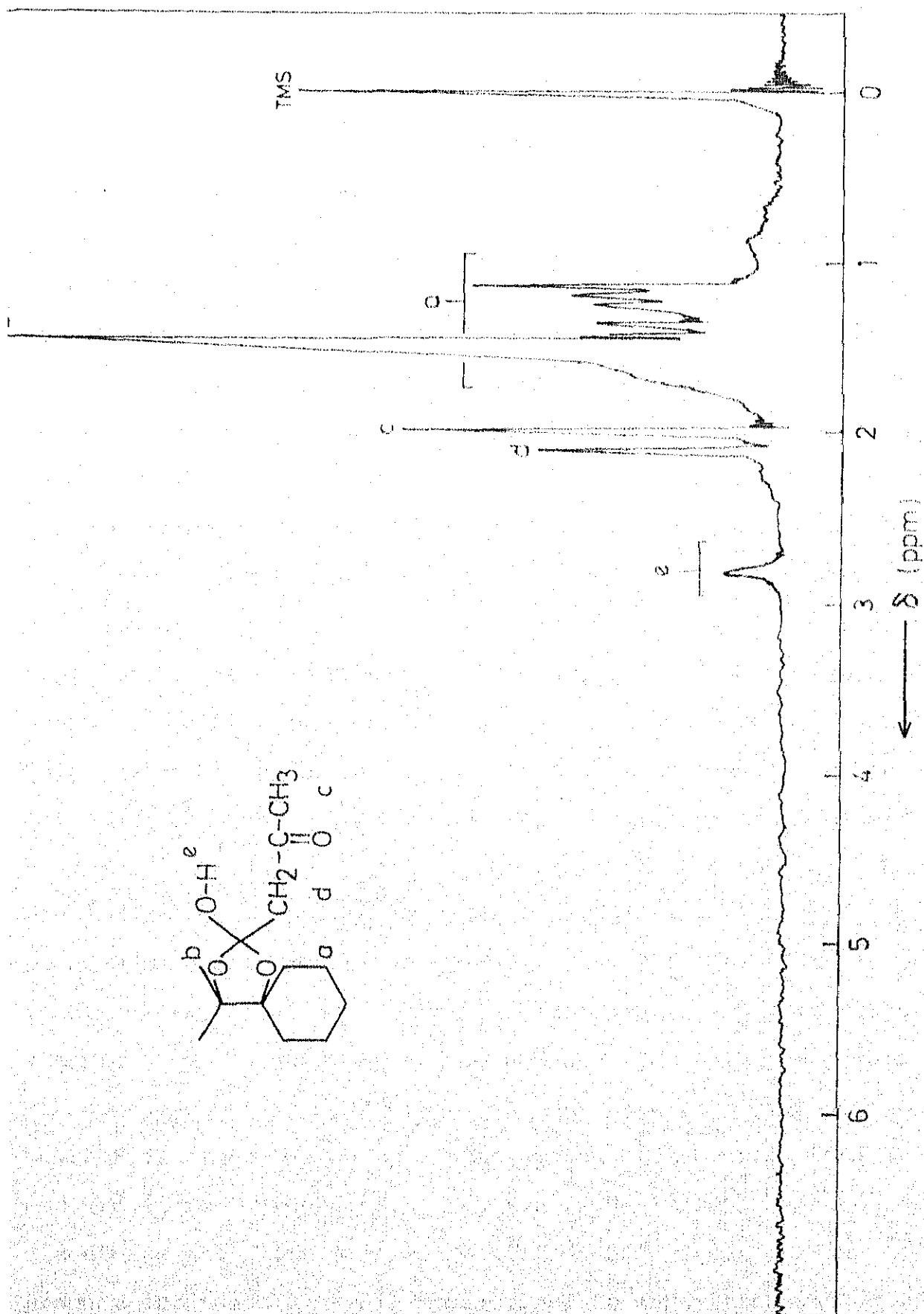
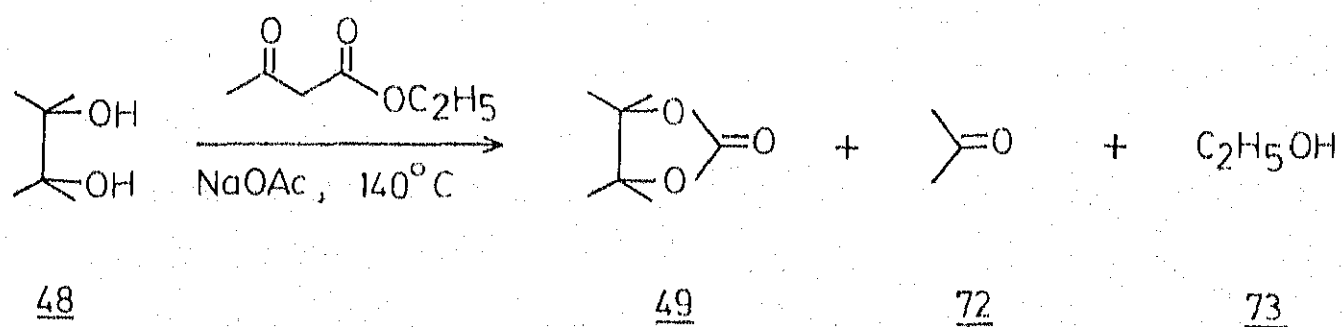
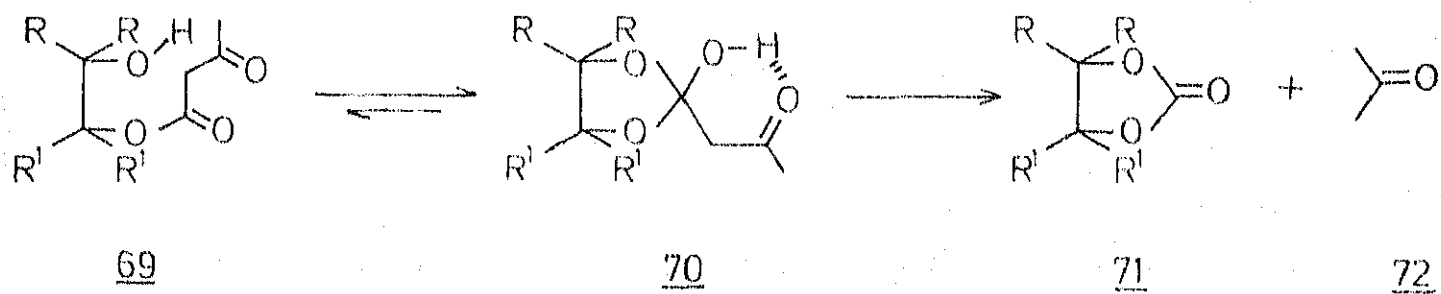


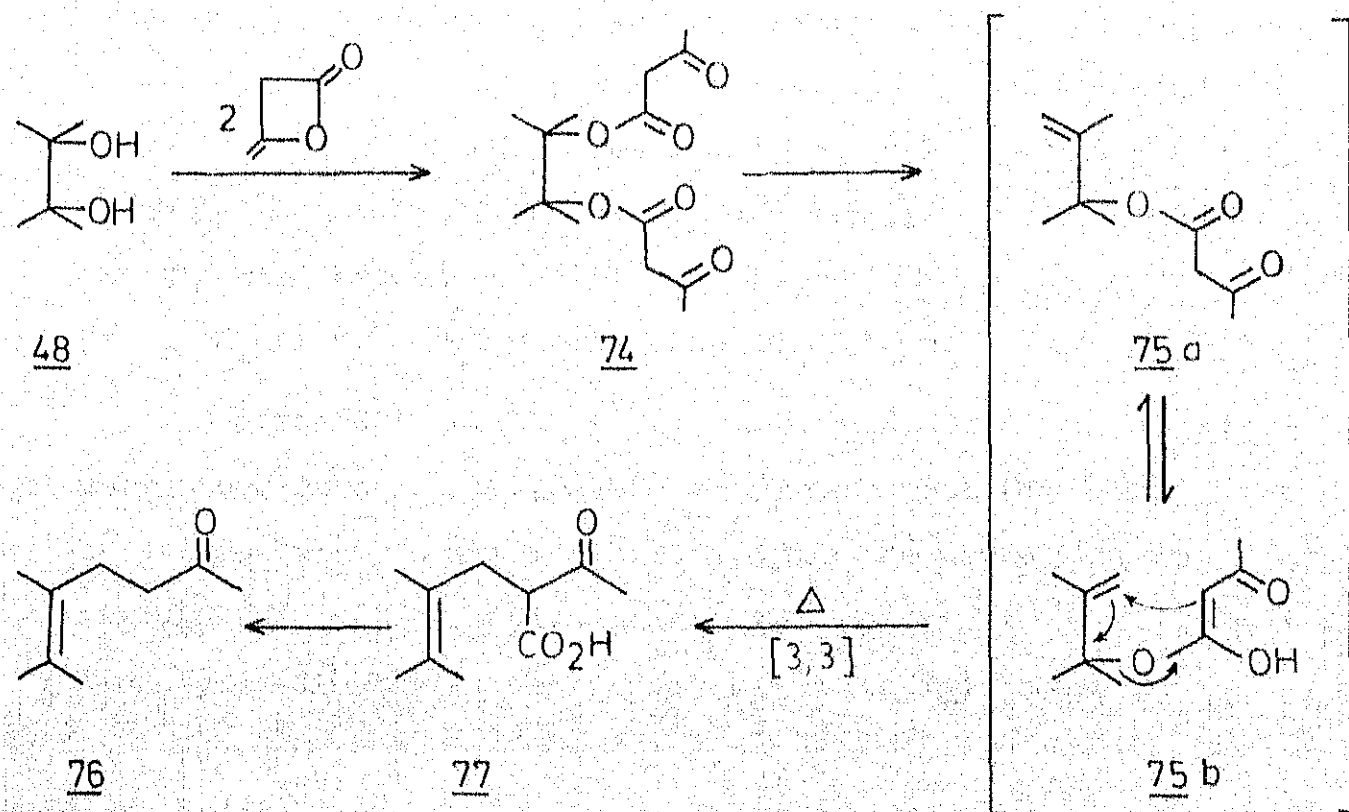
Fig. 1-A-8 ^1H NMR spectrum (60 MHz) of 68.

The cyclic carbonates are known in the literature^{65,68} and are prepared by either the ester interchange between the diol and diethyl carbonate in the presence of a catalytic amount of dry sodium methoxide⁶⁹ or by the reaction of phosgene with diols in the presence of antipyrène.⁷⁰ The isolation of monoacetoacetates 55, 64 and 68 in the reactions of 1,2-ditertiary diols studied, coupled with the fact that the monoacetoacetates were transformed into cyclic carbonates upon heating, suggest that the formation of cyclic carbonates might proceed via the corresponding monoacetoacetates. In analogy with the well known mechanism of the decarboxylation of acetoacetic acid, the formation of cyclic carbonate and acetone could be visualized from the cyclic form of the monoacetoacetate,⁷¹ which seem to exist in equilibrium with the monoacetoacetate (Scheme I.A.17). This is further supported by the fact that the cyclic carbonates have been obtained in the transesterification reaction of ethylacetoacetate and 1,2-ditertiary diols in the presence of a base such as sodium methoxide.⁷² This was independently confirmed by us when cyclic carbonate 49 was isolated in 50% yield in the reaction of pinacol 48 with ethylacetoacetate at ca. 140°C in the presence of anhydrous sodium acetate. When the preparation of monoacetoacetate of pinacol 48 was attempted employing one mole of diketene, using catalytic amount of anhydrous sodium acetate in refluxing benzene for 4 h, 2,3-dimethyl-butane-2,3-diacetoacetate (74), m.p. 135°C (lit.⁷³ 135°C), was the only product obtained. In this connection, we came across an

Scheme I.A.17



Scheme 1.A.18



interesting transformation, reported in the literature, of the diacetoacetate 74 to give 2,3-dimethyl-2-hepten-6-one (76), upon base treatment.⁷³ In the absence of any proposed mechanism by the authors, we presume that the transformation occurs probably through a [3,3] sigmatropic rearrangement as depicted in Scheme I.A.18.

As mentioned earlier, the monoacetoacetates exist in equilibrium with their cyclic form (60 \rightleftharpoons 70). The hydroxyl and the ketone absorptions in the IR spectra of monoacetoacetates further support this fact. The mass spectra of the monoacetoacetates show a fragment with m/e ($M^+ - 18$) indicating that dehydration is an important mode of fragmentation, which in turn can occur easily from the cyclised form of the monoacetoacetates. Isolation of the α, β -unsaturated carbonyl compound 54 in the reaction of pinacol 52 with Ac_2O /DMAP, further supports the fact, that an equilibrium does exist between the open chain and the cyclised form of the monoacetoacetates. The compound 54 can be formed by the dehydration of the cyclic orthoester. Based on all these experimental evidences, different mechanistic pathways may be proposed for the cyclic orthoester formation.

Before dealing with the proposed mechanisms, it is worthwhile to give a few introductory remarks about the 1-acyl salts of 4-dimethylaminopyridine. It has been observed that in mixtures of acetic anhydride and DMAP, appreciable quantities of 1-acetyl-4-dimethylaminopyridinium acetate (41) could be

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detected even in CDCl_3 and CD_2Cl_2 by lowering the temperature by PMR analysis.¹ Though the presence of 4-dimethylamino group is accompanied by the pronounced reduction of the carbonyl activation due to the mesomeric stabilization, it is more than compensated by the greater availability of the cation in the ion pair, which facilitates the attack of an external nucleophile. Thus DMAP could be looked upon as the "catalytic support" for the electrophiles (nucleophilic catalysis). At the same time the acetate ion which is in the vicinity of the cation can cause an increase in the reaction rate by abstracting a proton from the nucleophile (general base catalysis).

The "path A" (Scheme I.A.19) utilizes the well established species 41¹ to form the monoacetate 79 which can cyclize to give the orthoacetate 82. This mode of cyclization has been demonstrated earlier by Hine *et al.* in the case of monotrifluoroacetate of pinacol 48.⁷⁴ The cyclic orthoacetate 82, on dehydration can give rise to the ketene cyclic acetal 81, which may react with 41 leading to the formation of 70 in the presence of an equivalent amount of water.

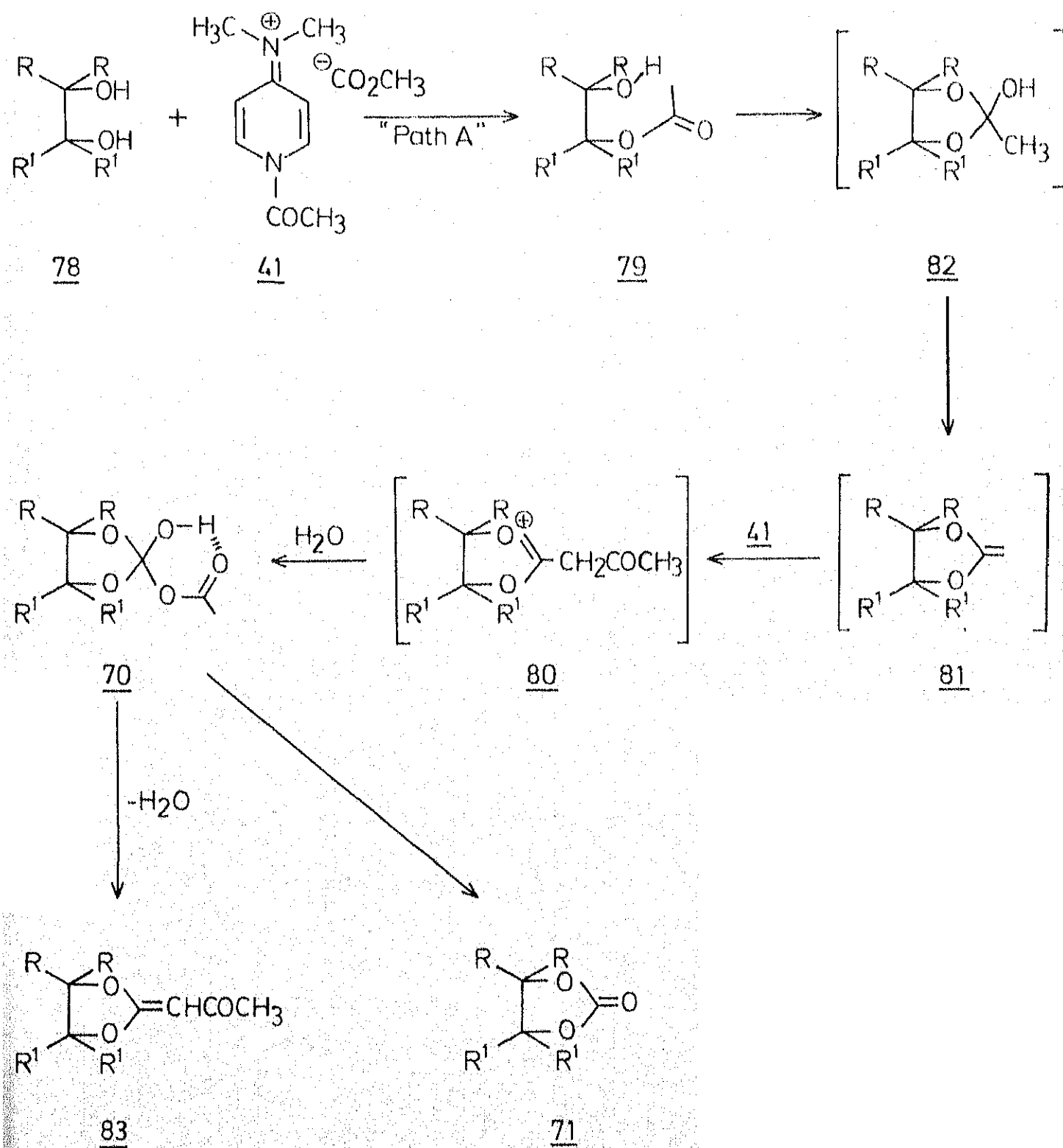
An alternative mode ("path B") for the formation of monoacetatoacetate 69 involves the intermediacy of ketene (Scheme - I.A.20) which in turn can come from 1-acetyl-4-dimethylaminopyridinium acetate (41). The ketene may react with the species 41 to give the 1-acetoacetyl-4-dimethylaminopyridinium acetate (86). The pinacol 78 on reaction with one equivalent of 86

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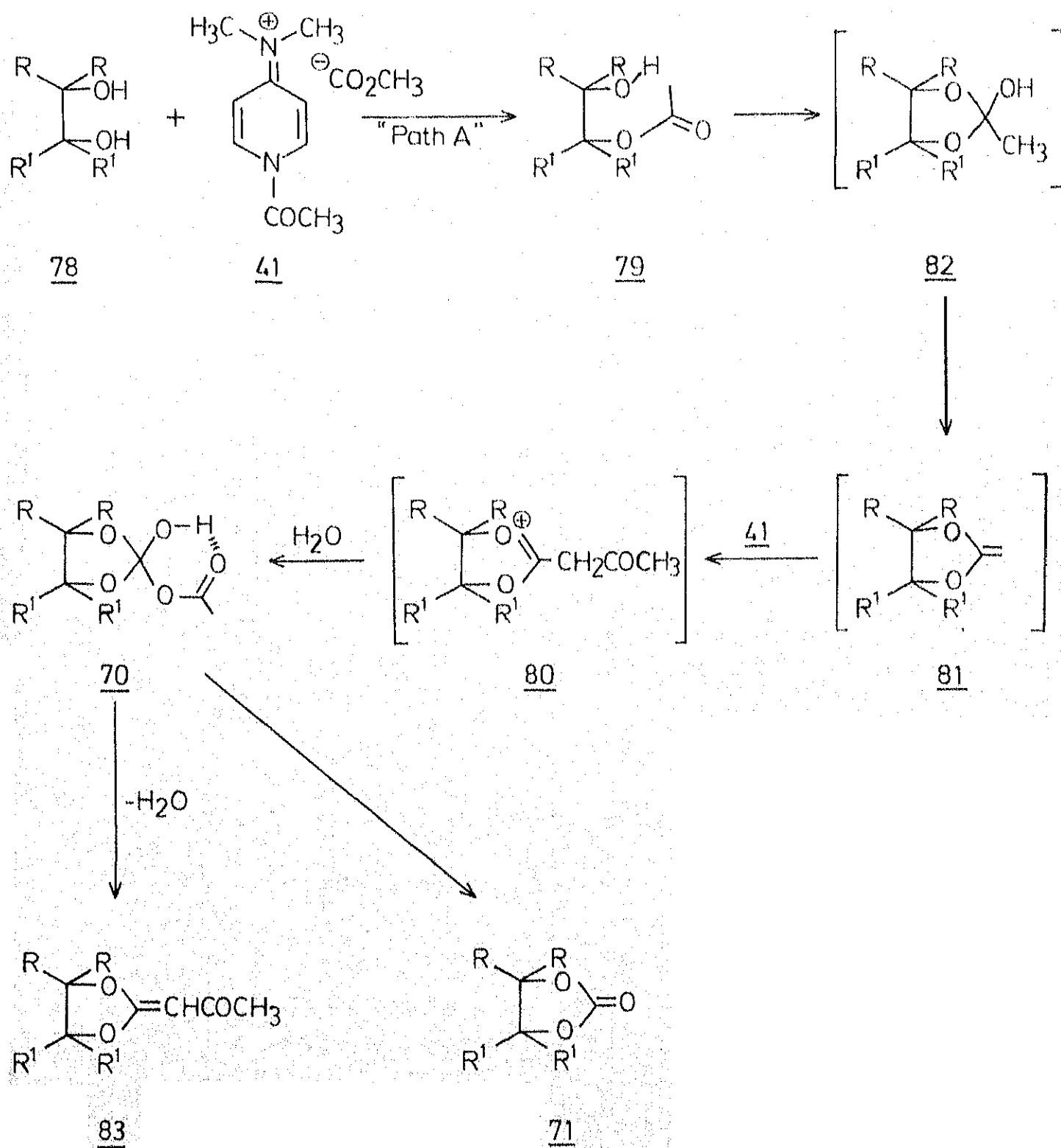
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An alternative mode ("path B") for the formation of monoacetatoacetate 69 involves the intermediacy of ketene (Scheme - I.A.20) which in turn can come from 1-acetyl-4-dimethylaminopyridinium acetate (41). The ketene may react with the species 41 to give the 1-acetoacetyl-4-dimethylaminopyridinium acetate (86). The pinacol 78 on reaction with one equivalent of 86

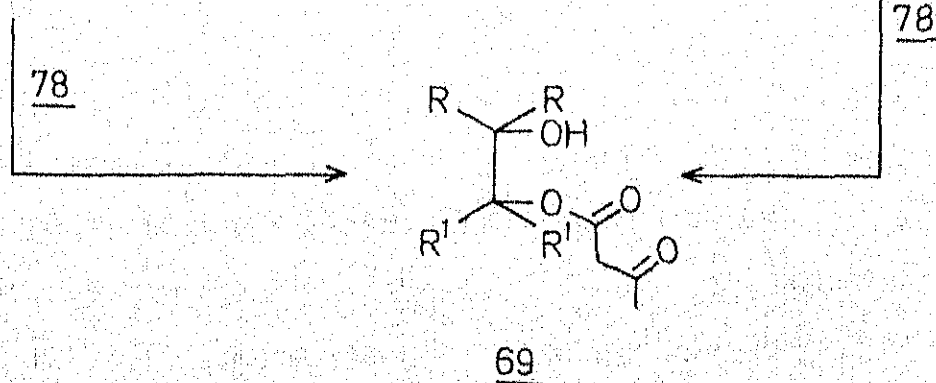
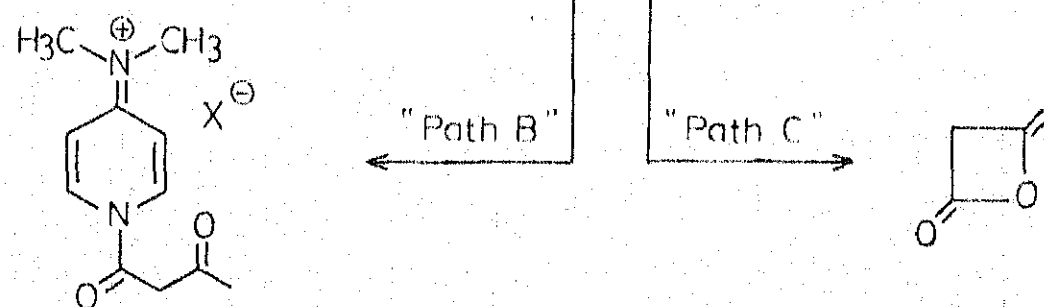
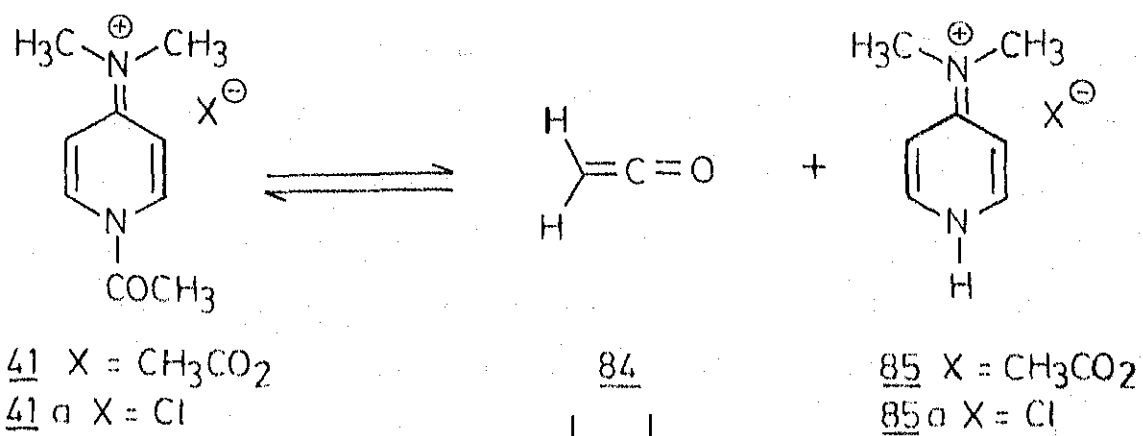
Scheme I.A.19



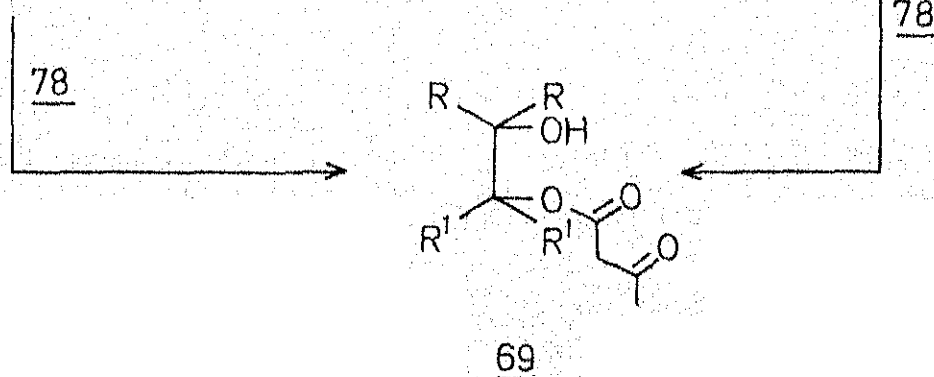
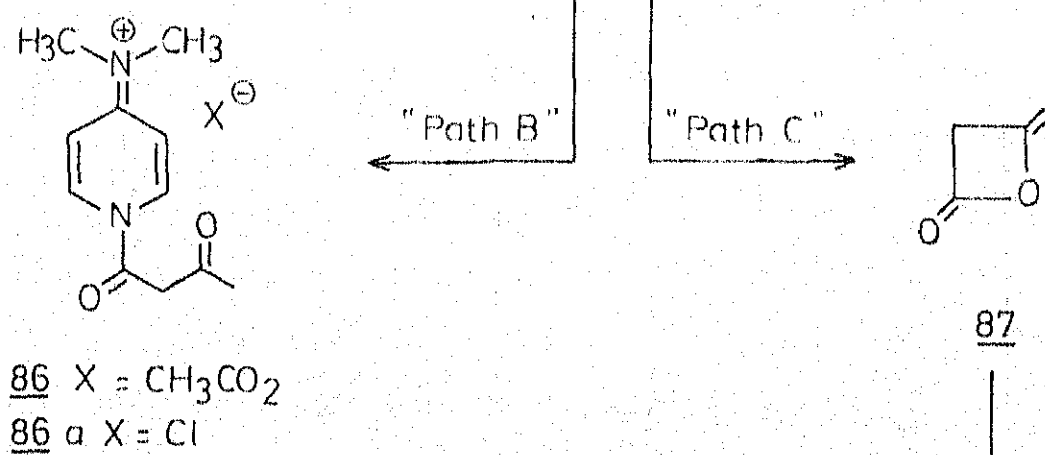
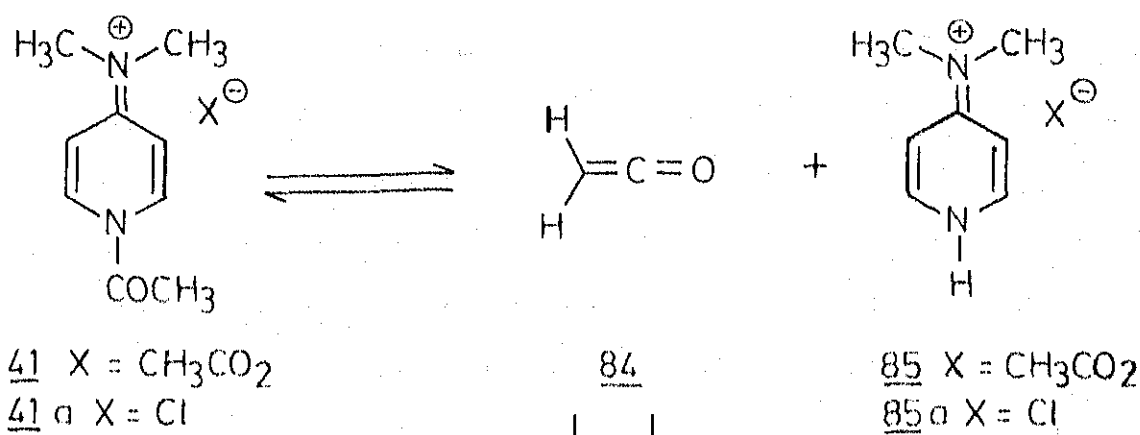
Scheme I.A.19



Scheme I-A-20



Scheme I-A-20



can give rise to the monoacetoacetate 69.

Yet another pathway ("path C") to rationalise the unusual products formed in the reaction of 1,2-ditertiary diols with acetic anhydride and DMAP at high concentration, would be via the intermediacy of diketene 87 obtained from the dimerization of ketene which in turn can come from 1-acetyl-4-dimethylamino-pyridinium acetate (41). The pinacol 78 on reaction with diketene can form the monoacetoacetate 69 (Scheme I.A.20).

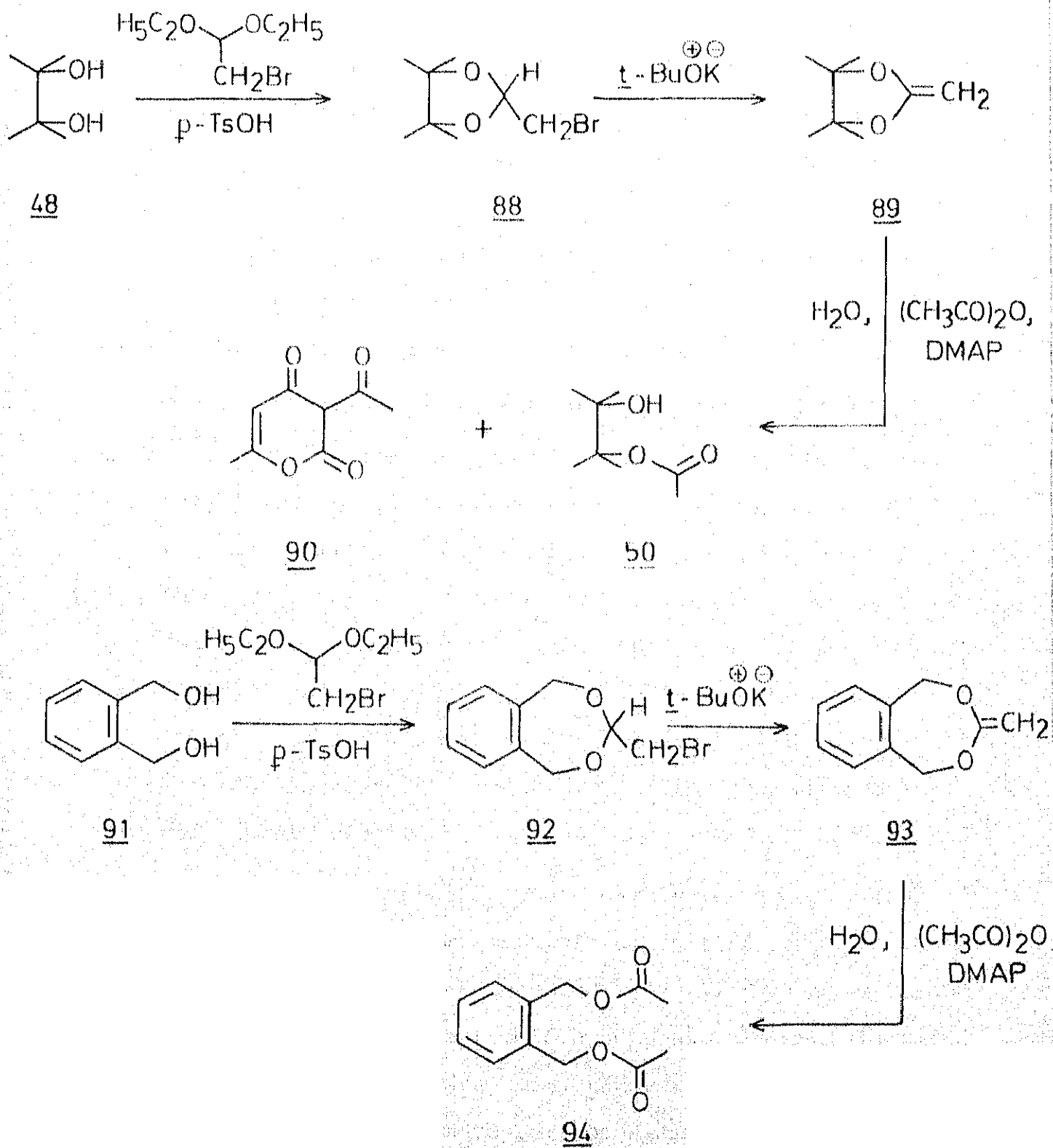
In order to test the validity of the mechanisms proposed, experiments were carried out with the ketene cyclic acetals 89 and 93 (Scheme I.A.21). The compound 2-methylene-4,4,5,5-tetramethyl-1,3-dioxolane (89) was prepared by the dehydrobromination of 2-bromomethyl-4,4,5,5-tetramethyl-1,3-dioxolane (88) using potassium tertiary butoxide.^{75,76} The compound 88 was in turn prepared from the transesterification reaction of bromoacetaldehyde diethylacetal⁷⁷ and pinacol 48 in the presence of a catalytic amount of p-toluenesulphonic acid. When 89 was treated with acetic anhydride and DMAP at 80°C for 2 h, followed by the addition of an equivalent amount of water, two products were obtained. Similarly when the reaction was carried out in dichloromethane at room temperature, identical products were obtained. One of the products was identified as the pinacol monoacetate 50 based on the spectral data. The other product 90, m.p. 111-112°C was identified as dehydroacetic acid based on PMR and mass spectral data. This compound did not depress

can give rise to the monoacetoacetate 69.

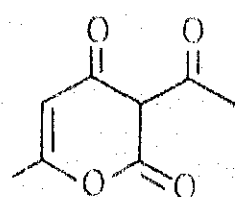
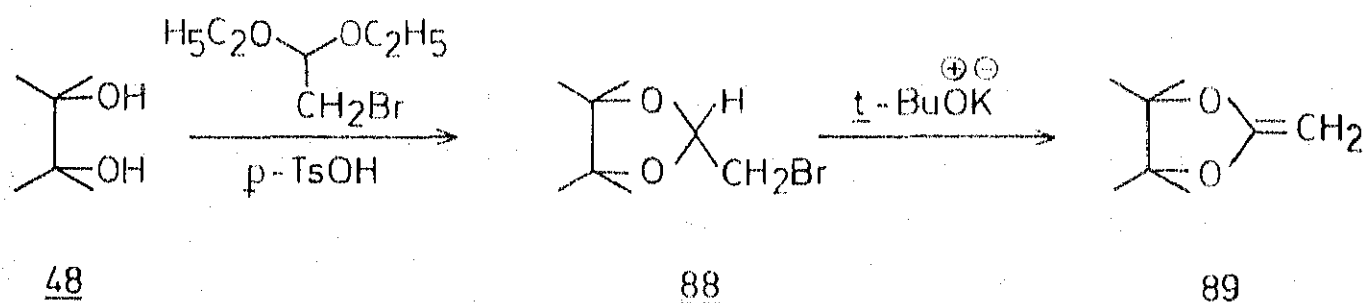
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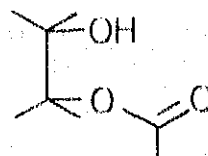
Scheme I.A.21



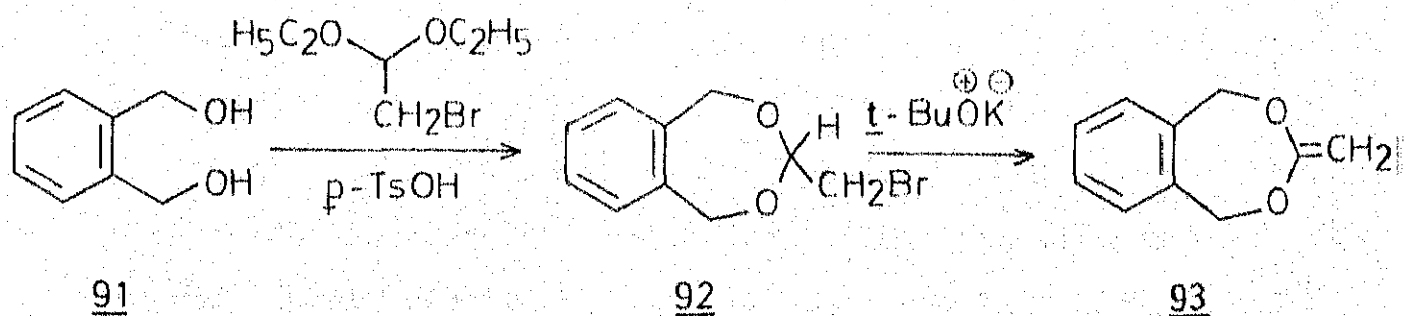
Scheme I.A.21



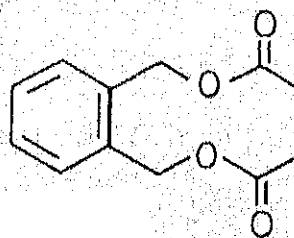
+



$\xrightarrow[\text{DMAP}]{\text{H}_2\text{O}, (\text{CH}_3\text{CO})_2\text{O}}$

9050

$\xrightarrow[\text{DMAP}]{\text{H}_2\text{O}, (\text{CH}_3\text{CO})_2\text{O}}$

94

the melting point of an authentic dehydroacetic acid in mixture melting point determination. In contrast, when 1,5-dihydro-3-methyleno-2,4-benzodioxepin (93)⁷⁸ was treated with acetic anhydride and DMAP, a 58% yield of the corresponding diacetate 94 was the only product isolated, m.p. 35°C, (mixture m.p.⁷⁹ 35°C). The formation of the acetylation products obtained in the two cases of ketene cyclic acetals studied could be rationalized in terms of the greater reactivity of the primary hydroxyl group relative to the tertiary hydroxyl group (Scheme I.A.21).

Thus "path A" involving the ketene cyclic acetal 81 as an intermediate in the formation of monoacetoacetate 70 could be safely ruled out since neither the monoacetoacetate 70 nor the products derived from it could be isolated in the reaction of authentic ketene acetal 81 under the same reaction conditions. The isolation of dehydroacetic acid (90) as one of the products could possibly be explained by invoking 'ketene' as an intermediate, as visualised in "path B" or "path C". Ketene dimerization to diketene and diketene dimerization to dehydroacetic acid under basic conditions are well documented in literature.⁸⁰

The mechanistic pathway 'B' invokes the intermediacy of 1-acetoacetyl-4-dimethylaminopyridinium salt 86 presumed to be formed by the reaction of ketene and 1-acetyl-4-dimethylaminopyridinium salt 41. To test this hypothesis, ketene generated independently through a ketene generator⁸¹ was passed into a solution of 1-acetyl-4-dimethylaminopyridinium chloride (41a)⁸²

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in dichloromethane in the presence of a catalytic amount of DMAP at room temperature. After stirring for 0.5 h, the solvent was removed and the residue was thoroughly washed with ether-petroleum ether (1:1) to remove the excess ketene. The PMR spectrum of this red residue did not show the formation of 1-acetoacetyl-4-dimethylaminopyridinium chloride (86a). In order to rule out the possibility of "path B" totally, 1-methylcyclohexanol (3) was treated with a solution of this red residue in dichloromethane in the presence of a catalytic amount of DMAP. However, no reaction occurred and the tertiary alcohol was recovered unchanged quantitatively along with a small amount of dehydroacetic acid (90). If "path B" were to operate, we would have obtained at least some of the 1-methylcyclohexyl acetoacetate (96). The dehydroacetic acid (90) got in this reaction could have come from polymerization of ketene.

The isolation of dehydroacetic acid (90) in the reaction of Ac_2O /DMAP with ketene cyclic acetal 89 led us to think that the diketene, precursor to 90 might have come from acetic anhydride and DMAP, according to our proposed mechanistic pathway 'C'. With a view to confirming this, acetic anhydride and 4-dimethylaminopyridine were mixed in equivalent amounts and left to stand at room temperature for two days. The regular work up gave a reddish brown liquid, from which dehydroacetic acid (90) was obtained as the only isolable product.

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In order to substantiate the intermediacy of diketene in these reactions, 1-methylcyclohexanol (3) was treated with acetic anhydride (2.2 equivalents) and 4-dimethylaminopyridine (1 equivalent), in the absence of solvent at ca. 85°C for 4 h, which afforded 1-methylcyclohexyl acetate (95) and 1-methylcyclohexyl acetoacetate (96) in the ratio of 10:3.1, along with a small amount of unchanged starting material 3. The acetate 95 showed an ester carbonyl absorption at 1735 cm^{-1} in the IR spectrum. The PMR spectrum indicated a multiplet centred at δ 1.5 (13H) due to the methyl and the methylene protons and a singlet at 2.06 (3H) assigned to the methyl protons. The structure was further confirmed by preparing the authentic acetate by the reported procedure³ and comparing the IR and the PMR spectra. The acetoacetate 96 showed IR absorptions at 1710 and 1735 cm^{-1} , characteristic of the keto and the ester groups, respectively. The PMR spectrum indicated a multiplet centred at δ 1.41 (13H) corresponding to the methyl and the methylene protons, a singlet at 2.33 (3H) due to the methyl protons and another singlet at 3.42 (2H) which can be assigned to the methylene protons (Fig. I.A.9). The mass spectrum showed a molecular ion peak at m/e 198. The identical spectra obtained for 96 and that prepared by the reaction of 3 with diketene proves the structural assignment beyond doubt. The formation of acetoacetate 96 can be explained only through the intermediacy of diketene in the reaction and acetate might have been formed

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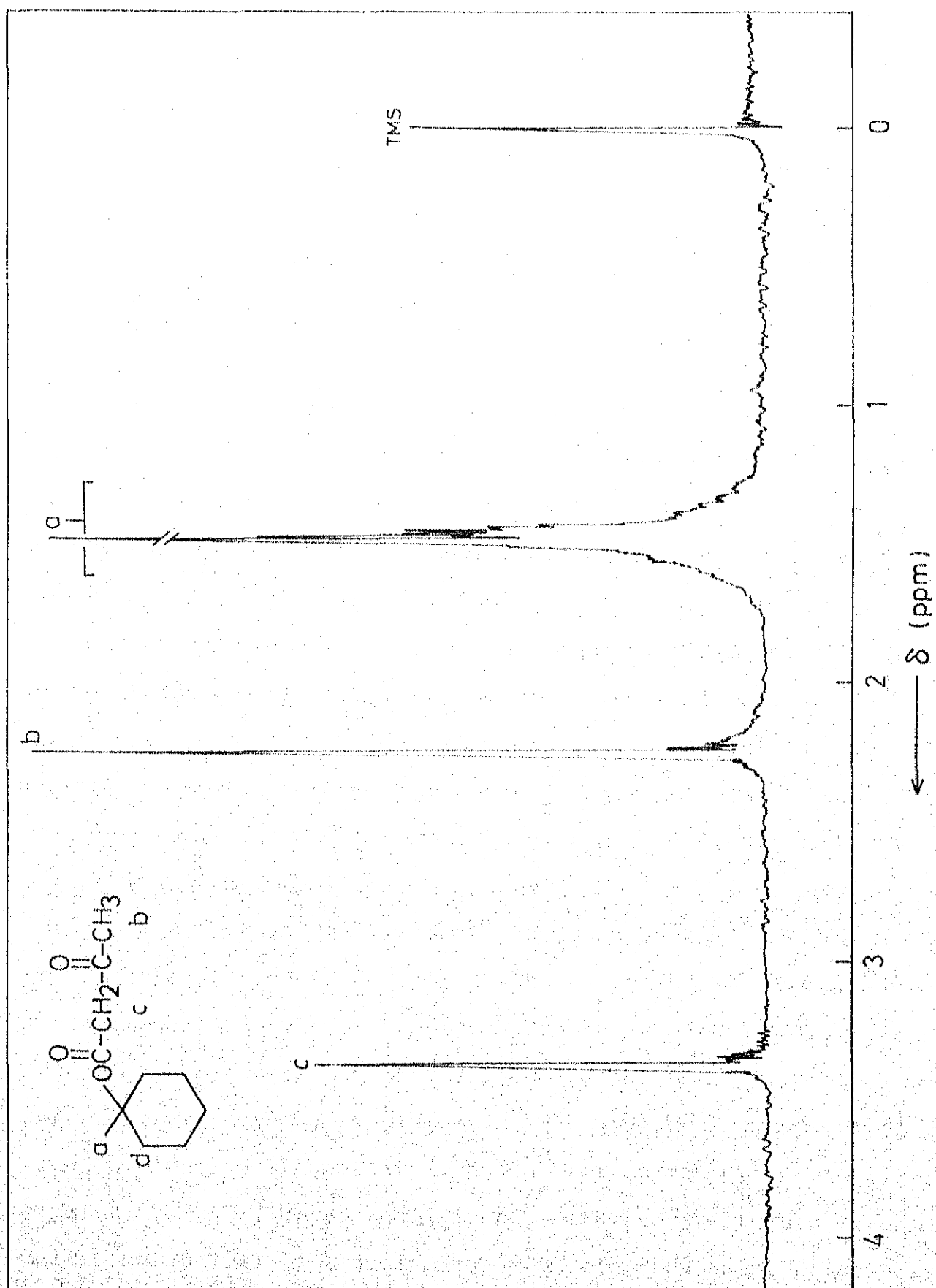


Fig. I.A.9 ^1H NMR spectrum (100 MHz) of 96.

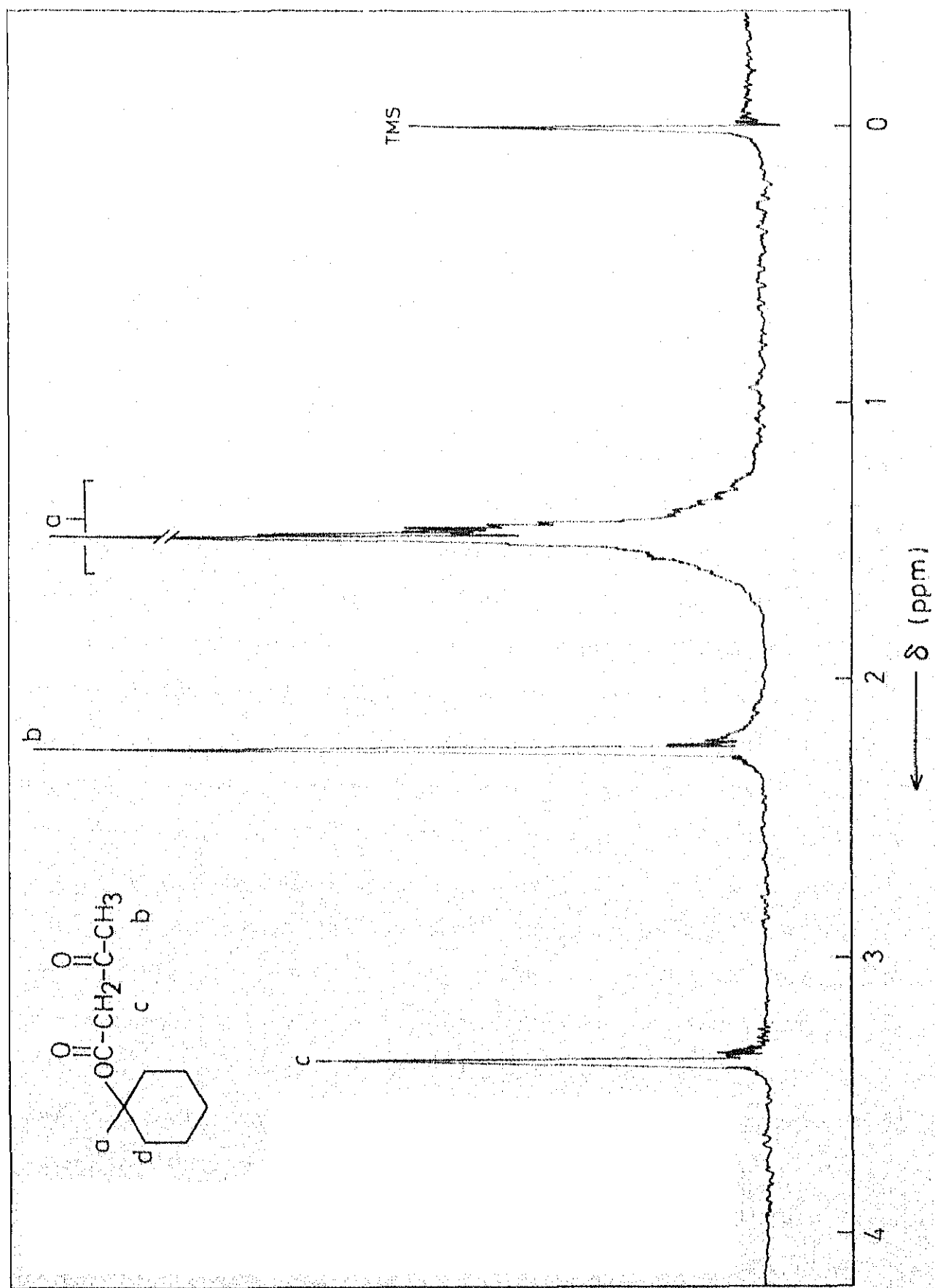


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from the reaction of alcohol 3 with ketene or through the nucleophilic attack of the alcohol 3 on the species 41. In order to examine the generality of the reaction with the tertiary alcohols, experiments were carried out with other carbiniols such as 2-phenylpropan-2-ol (97) and 1,1-diphenylethanol (100).

When 97 was treated with acetic anhydride and DMAP at ca. 85°C for 4 h, a mixture of products was obtained (Scheme - I.A.22). Purification of the crude product by flash chromatography yielded 2-acetoxy-2-phenylpropane (98) and 2-acetoacetoxy-2-phenylpropane (99) in the ratio of 2.2:1. The acetate 98 showed an IR absorption at 1735 cm^{-1} characteristic of the ester carbonyl group. The PMR spectrum indicated a singlet at $\delta 1.65$ (6H) assigned to the methyl group protons, a singlet at 1.88 (3H) due to the methyl protons and a broad multiplet centred at 7.25 (5H) corresponding to the aromatic protons. The mass spectrum showed a peak at m/e 118 ($M^+ - \text{CH}_3\text{COOH}$). The structure of the acetate was further confirmed by making an authentic sample by the reported procedure and comparing the IR and the PMR spectra.³ The acetoacetate 99 showed strong IR absorptions at 1715 and 1740 cm^{-1} , characteristic of the keto and the ester groups. The PMR spectrum showed a singlet at $\delta 1.84$ (6H) due to the methyl group protons, a singlet at 2.26 (3H) for the methyl protons, a singlet at 3.45 (2H) assigned to the methylene protons and a multiplet at 7.43 (5H) due to the aromatic protons (Fig. I.A.10). The

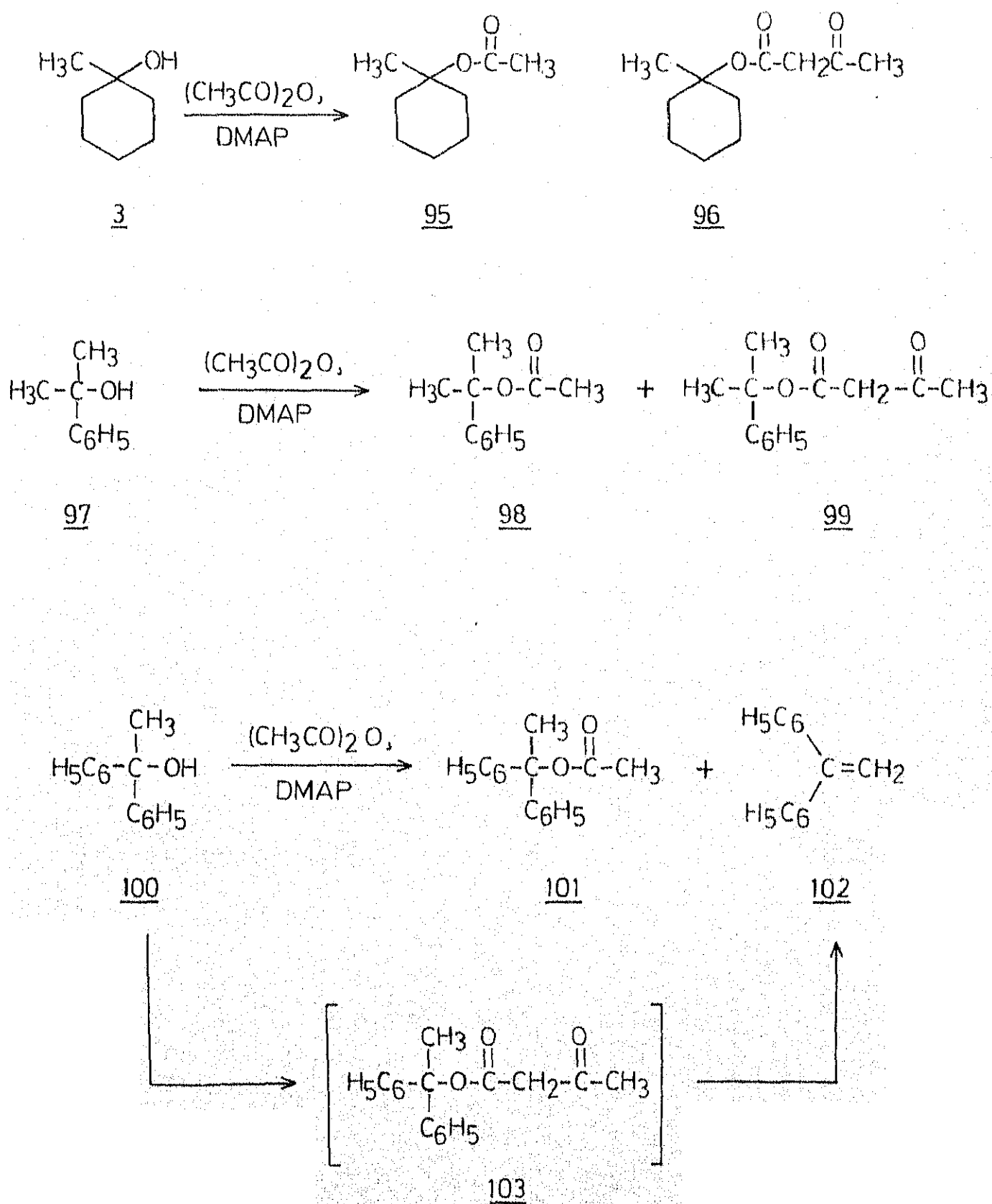
83800

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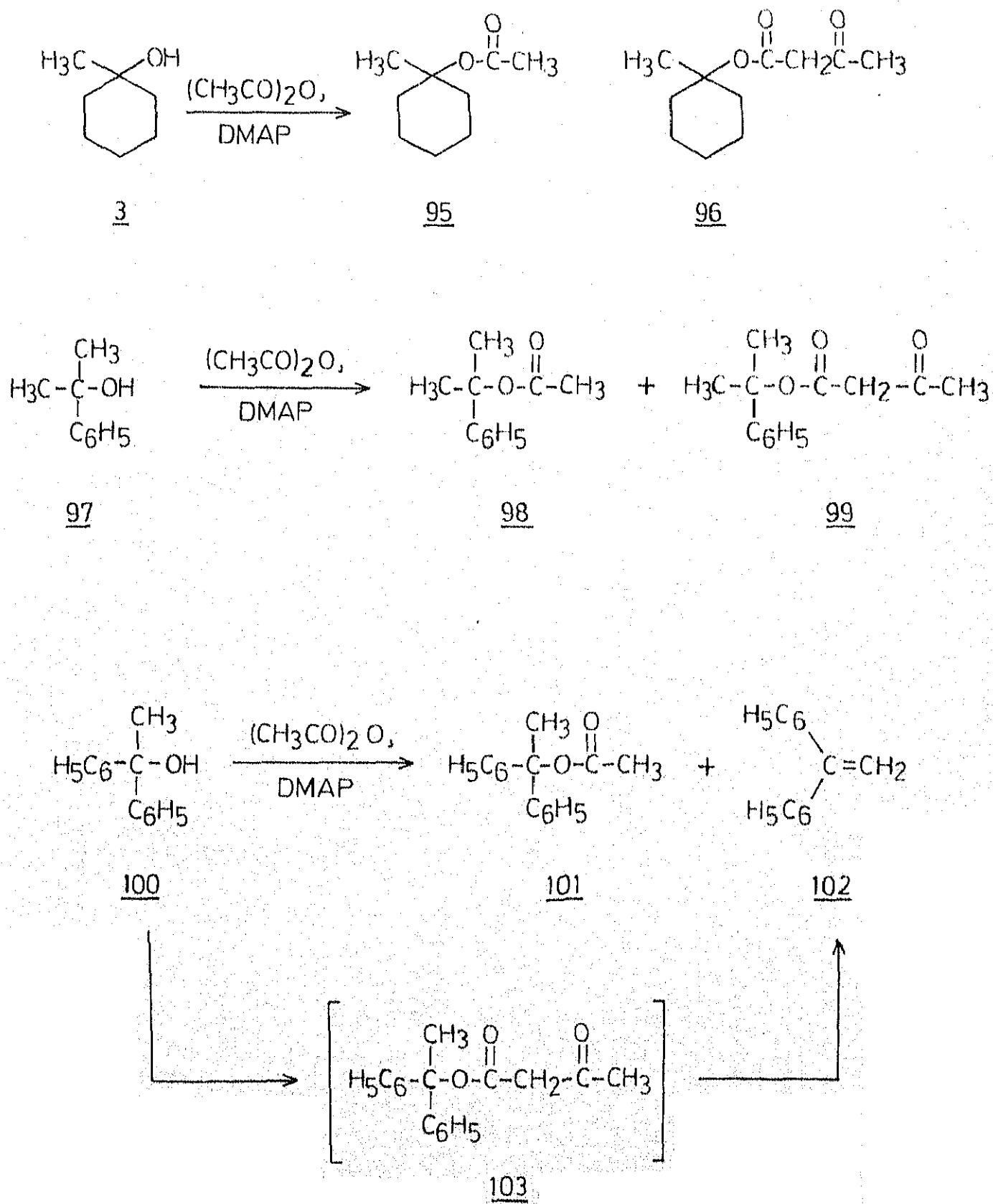
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Scheme I.A.22



Scheme I.A.22



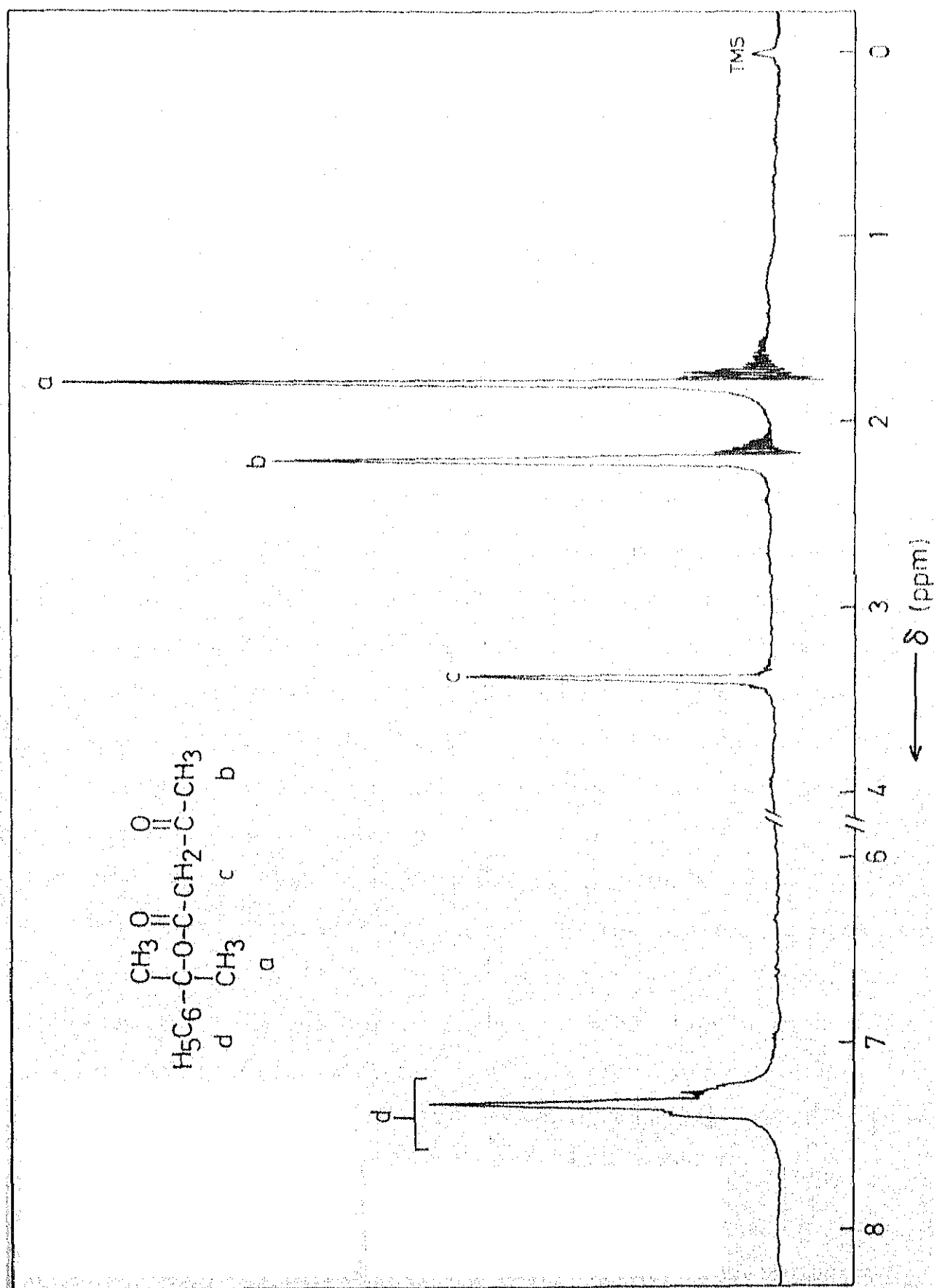


Fig. I-A-10 ^1H NMR spectrum (100 MHz) of 99.

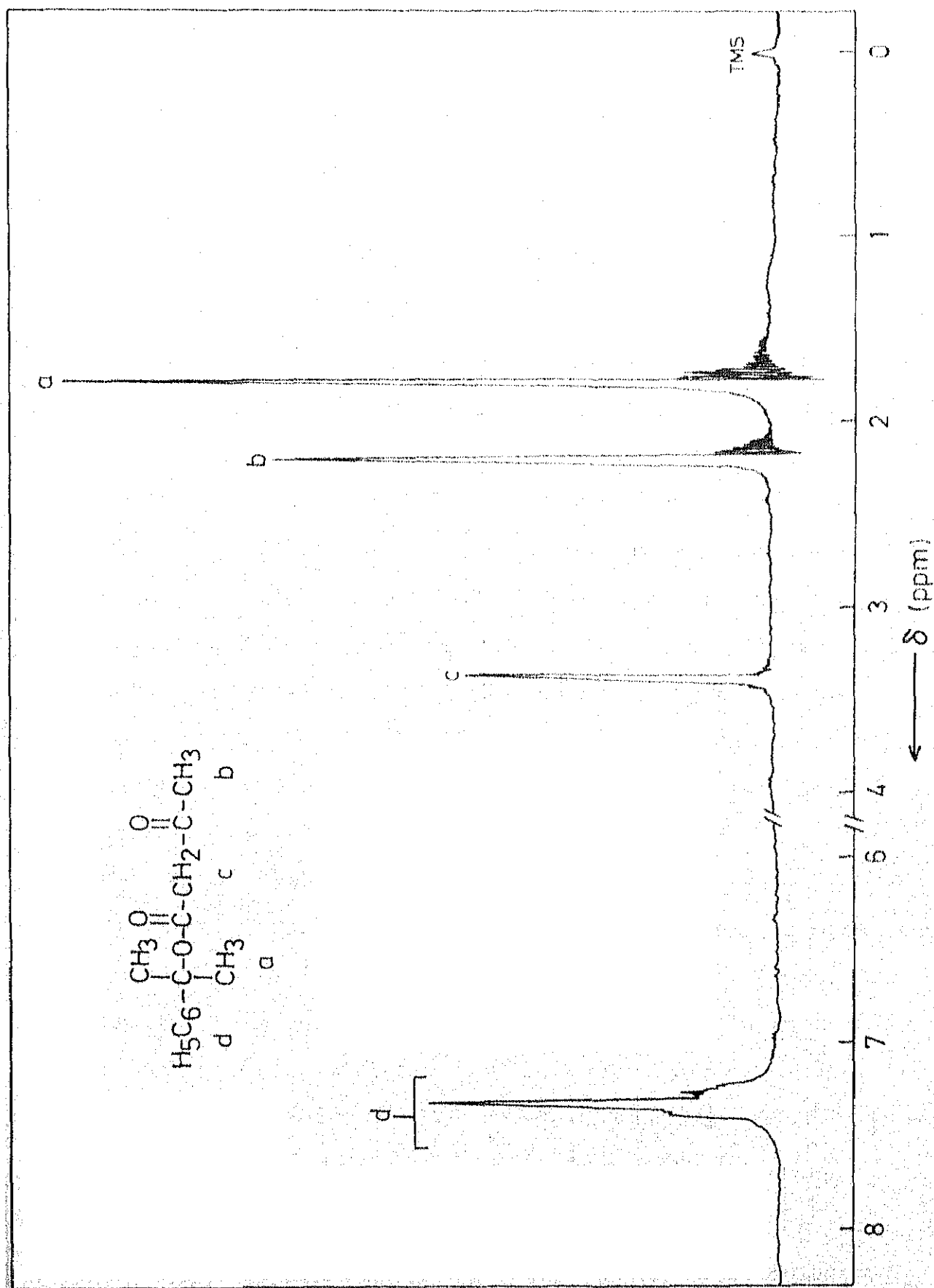


Fig. I.A.10 ^1H NMR spectrum (100 MHz) of 99.

mass spectrum gave a molecular ion peak at m/e 220. The formation of the acetoacetate was further confirmed by preparing an authentic sample by reacting the alcohol 97 with diketene and comparing the IR and the PMR spectra.

However, when 1,1-diphenylethanol (100) was treated with acetic anhydride and dimethylaminopyridine under analogous conditions, 1,1-diphenylethyl acetate (101) and 1,1-diphenylethylene (102) were obtained in 46% and 52% yield, respectively. The IR spectrum of acetate 101 showed absorption at 1740 cm^{-1} characteristic of the ester carbonyl group. The PMR spectrum showed a singlet at $\delta 2.09$ (3H) due to the methyl group protons, a singlet at 2.19 (3H) assigned to the methyl protons and another singlet at 7.2 (10 H) corresponding to the aromatic protons. The spectral data of the acetate 101 were identical with that reported in the literature.⁸³ The IR spectrum of the olefin 102 showed absorptions at 1600 and 1660 cm^{-1} characteristic of the carbon-carbon double bond. The PMR spectrum showed a singlet at $\delta 5.39$ (2H) assigned to the olefinic protons and a singlet at 7.23 (10 H) due to the aromatic protons. The structure was further confirmed by comparison with the spectra of authentic 1,1-diphenylethylene. The olefin 102 possibly might have come from the elimination reaction of the acetoacetate 103.⁸⁴

The formation of acetoacetates in the case of tertiary alcohols provides strong evidence for the intermediacy of

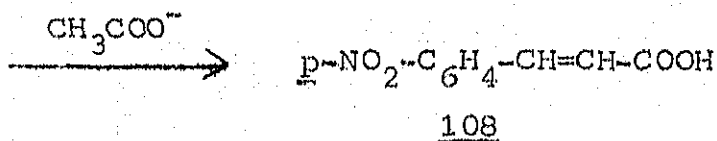
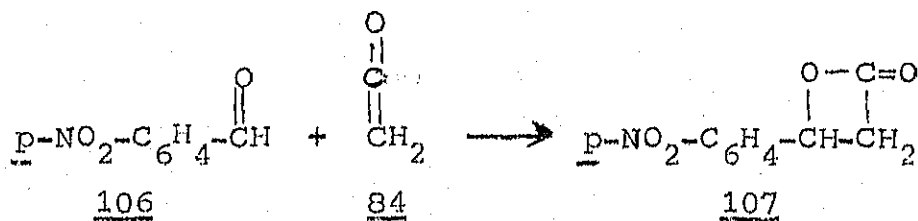
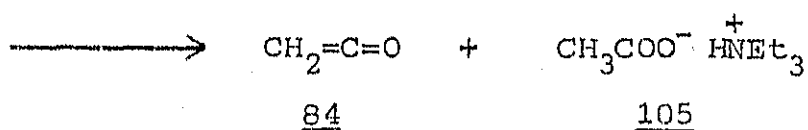
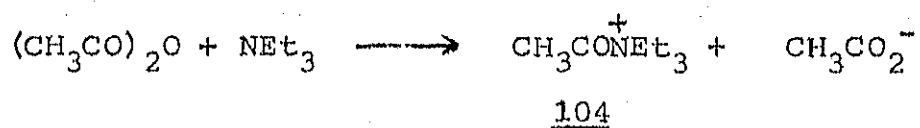
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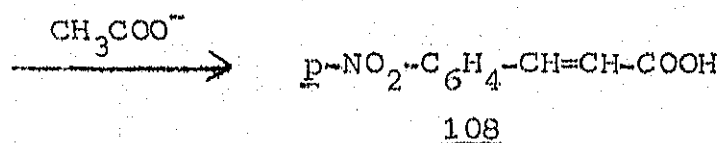
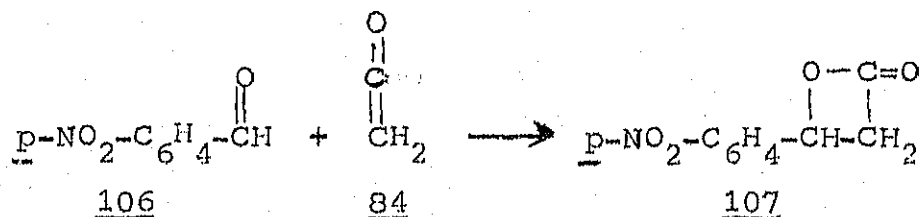
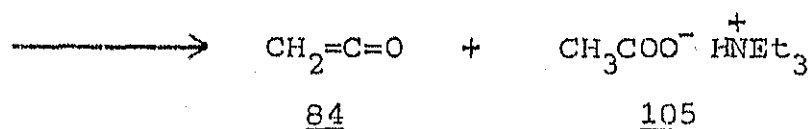
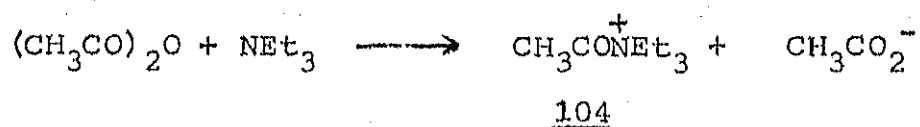
Scheme I.A.23



With a view to examining the generality of the reaction with the anhydrides, the pinacol 48 was treated with 4-dimethylaminopyridine and propionic anhydride. Interestingly, a mixture of two products was obtained (Scheme I.A.24). The crude product upon flash chromatography yielded 72.0% of monopropionate 109.

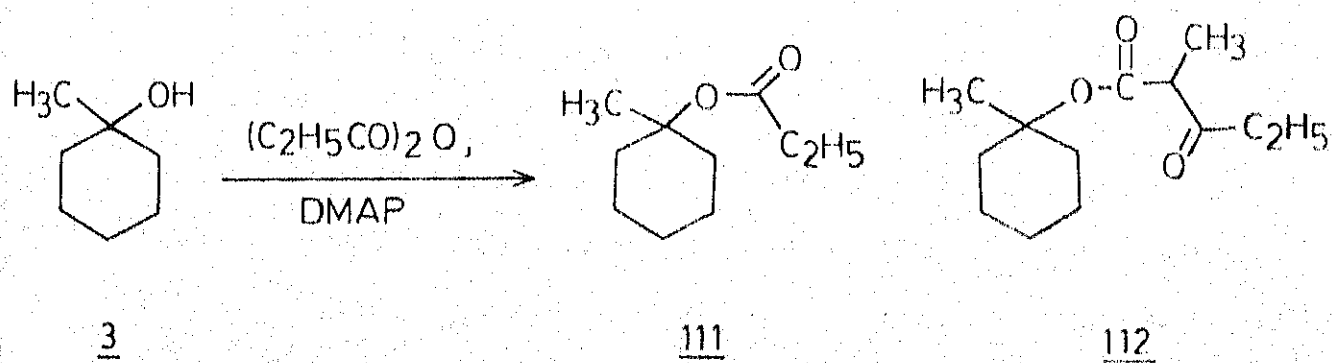
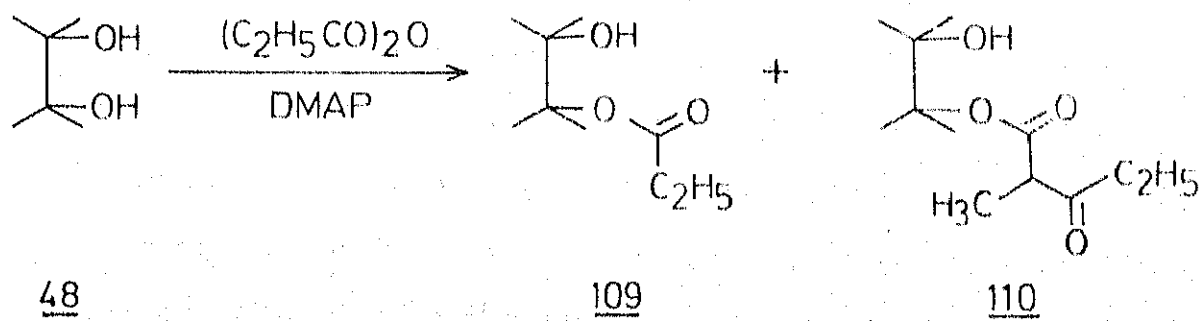
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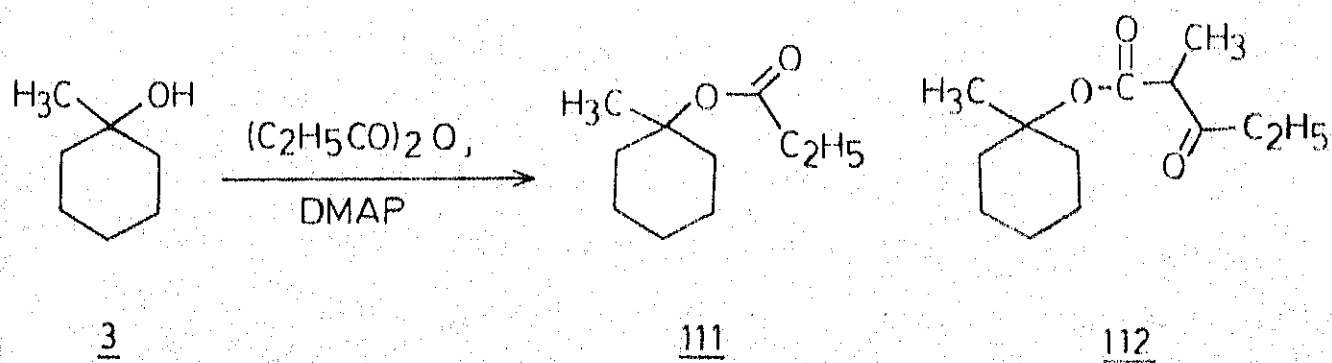
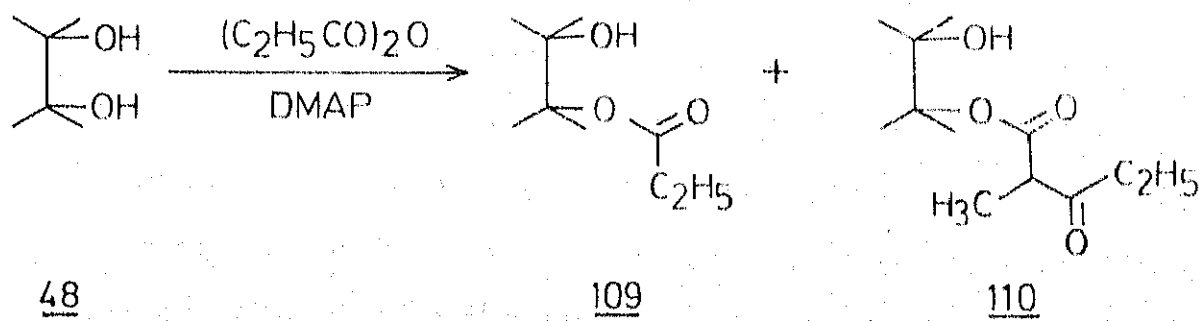
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Scheme I.A.24



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Encouraged by this result, a reaction was carried out with propionic anhydride and DMAP under identical conditions, with 1-methylcyclohexanol (3). As anticipated, a mixture of two products in the ratio of 2.8:1 was obtained (Scheme I.A.24). The crude product upon flash chromatography afforded a 75.0% yield of 1-methylcyclohexyl propionate (111), with the

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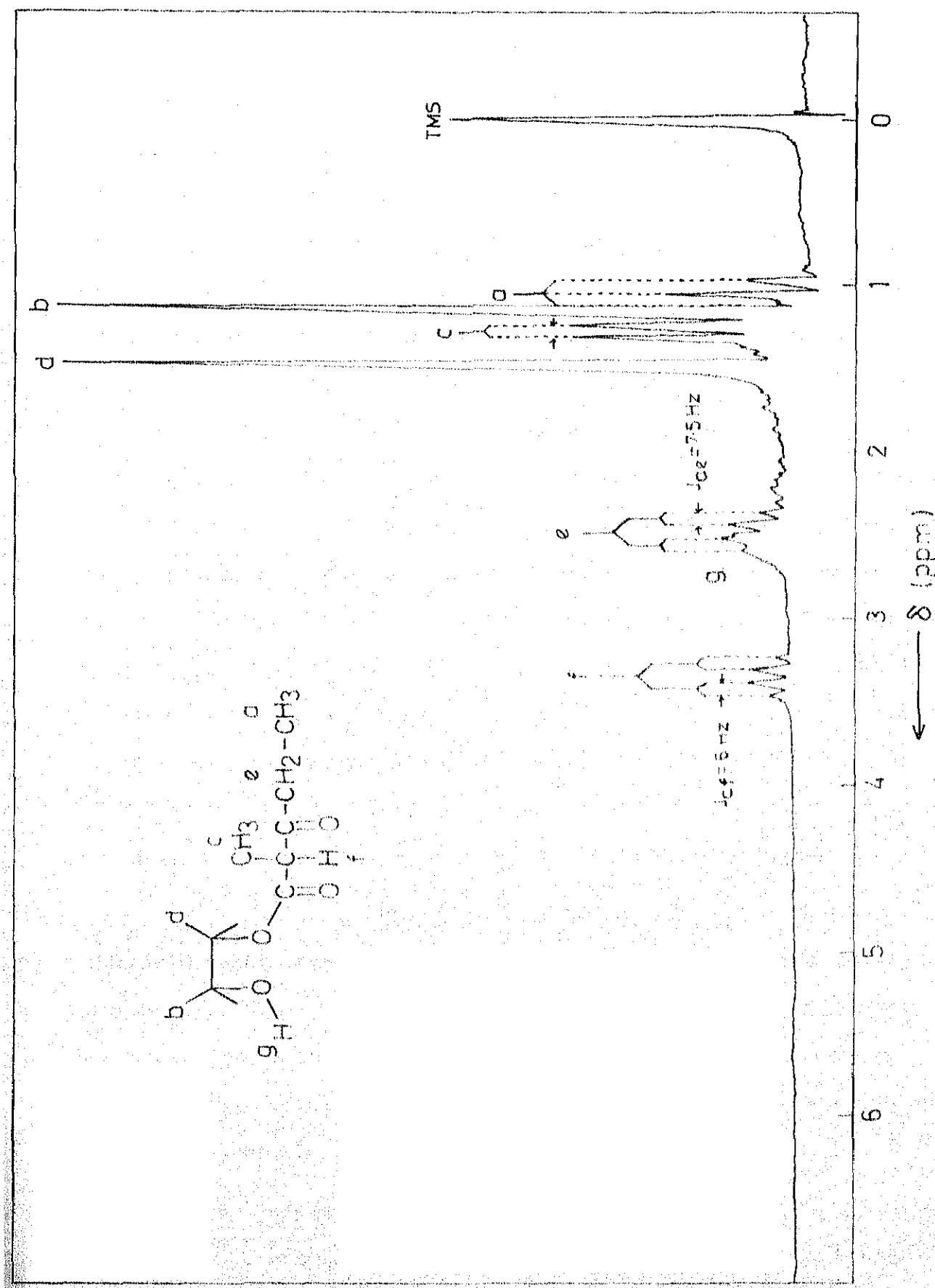


Fig. I.A.11 ^1H NMR spectrum (90 MHz) of 110.

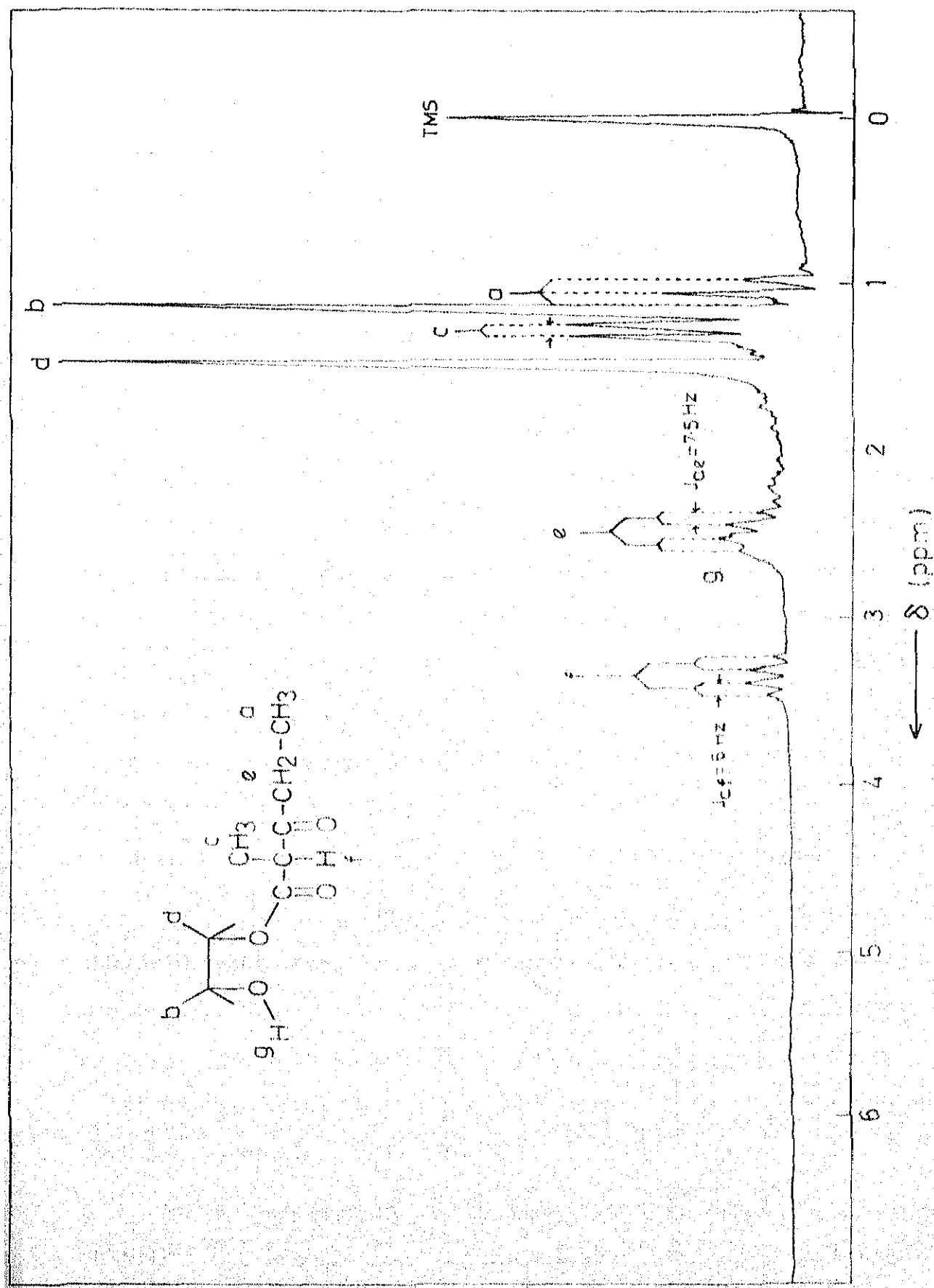


Fig. I.A.11 ^1H NMR spectrum (90 MHz) of 110.

characteristic IR absorption at 1730 cm^{-1} , typical of the ester carbonyl group. The PMR spectrum of 111 showed a triplet due to the methyl group protons at $\delta 1.1$ (3H, $J = 7\text{ Hz}$), a broad singlet at 1.43 (13H) assigned to the methyl and the methylene protons and a quartet at 2.23 (2H, $J = 7\text{ Hz}$), due to the methylene protons. The minor product 112 was obtained in 21% yield. The IR spectrum of 112 showed strong absorptions at 1710 and 1730 cm^{-1} , characteristic of keto and ester carbonyl groups, respectively. The PMR spectrum showed a triplet at $\delta 1.1$ (3H, $J = 6\text{ Hz}$), due to the methyl protons, a doublet at 1.3 (3H, $J = 6\text{ Hz}$), due to the methyl group protons, a broad singlet at 1.5 (13H) assigned to the methyl and the methylene protons. A quartet was indicated at 2.5 (2H, $J = 6\text{ Hz}$), due to the methylene protons and yet another quartet at 3.37 (1H, $J = 6\text{ Hz}$), assigned to the methine proton (Fig. I.A.12). All these data fit in well with the compound that would have been formed if 1-methylcyclohexanol (3) were to react with the methylketene dimer.

In contrast to the reaction of pinacol 48 with acetic anhydride and DMAP, no cyclic carbonate 49 was isolated in the reaction with propionic anhydride and DMAP. This only suggests that the cyclization of 110 to give the orthoester may be difficult in the latter case, which is necessary for the formation of carbonate.

In our experiments with 1-acetyl-4-dimethylaminopyridinium chloride (41a) some interesting observations were made during

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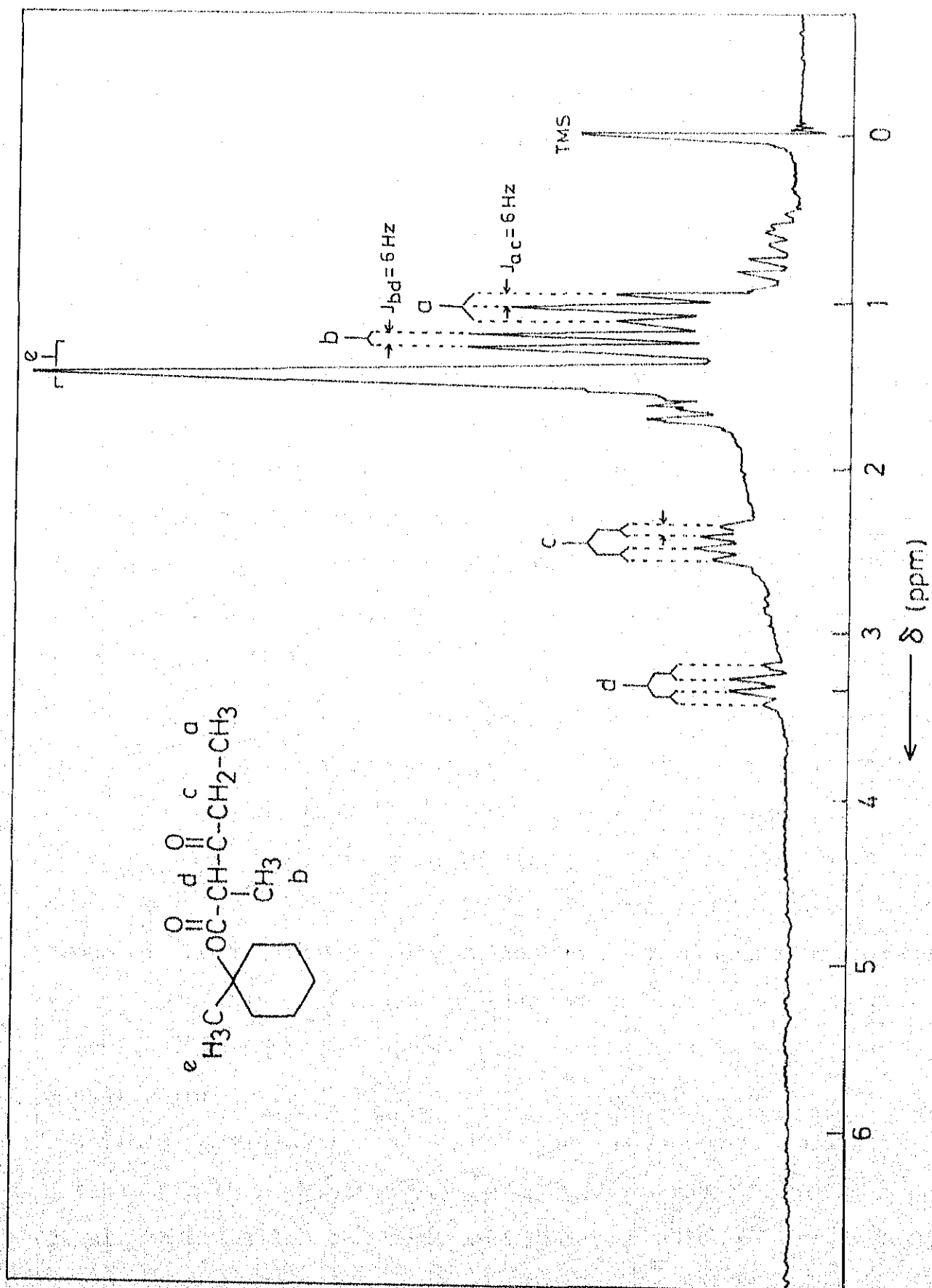


Fig. I-A-12 ^1H NMR spectrum (90 MHz) of 112.

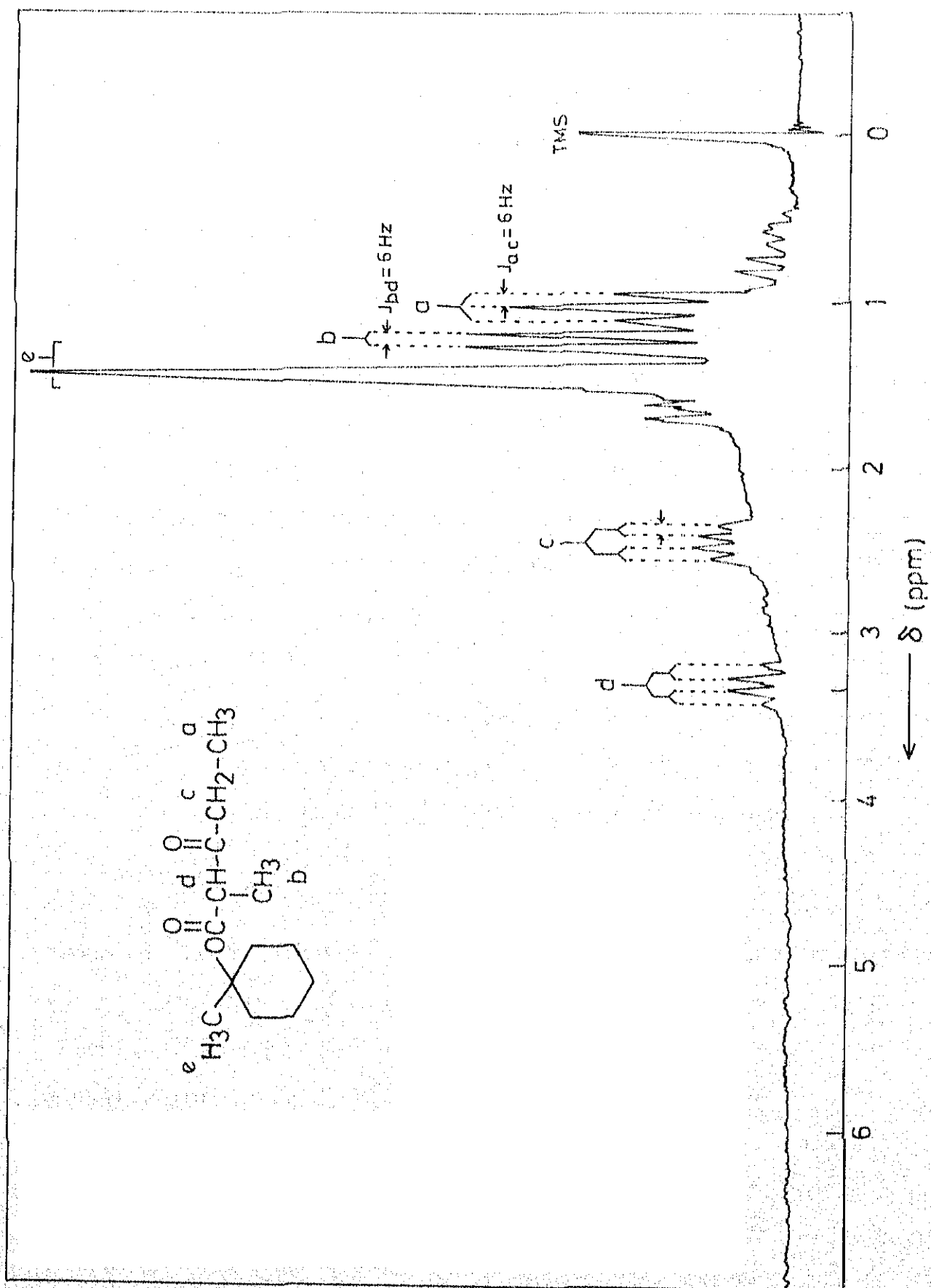


Fig. I.A.12 ^1H NMR spectrum (90 MHz) of 112.

PMR studies. When 1-acetyl-4-dimethylaminopyridinium chloride (41a) was dissolved in CDCl_3 and the PMR was recorded immediately, two equal intensity signals were obtained at δ 2.0 and 2.2. The intensity of the higher field signal continued to increase and the other continued to decrease as the time lapsed. The PMR taken after 2 h showed only one signal at δ 2.0. The other signals in the spectrum were a singlet at δ 3.15 (6H) due to the methyl protons and two doublets at 6.6 (2H) and 8.15 (2H) assigned to the aromatic protons. Another interesting feature observed in the PMR spectrum was the continuous shifting of a signal to downfield which originally appeared at δ 9.2. The signal seemed to rest at δ 16.0 when the PMR was repeated after 24 h (Fig. I.A.13).

These observations could be rationalised on the assumption that 1-acetyl-4-dimethylaminopyridinium chloride (41a) slowly decomposes in solution giving rise to ketene and hydrogen chloride. The absorption in the PMR spectrum at δ 2.0 might be due to the protons of ketene and that at δ 2.2 due to the methyl group of the N-acetyl moiety which seems to decrease in intensity with time. This is further substantiated by the fact that freshly prepared ketene shows a sharp singlet at δ 2.0 in deuteriochloroform. The reason why the signal at δ 9.2 shifts downfield continuously and without any change in intensity is not quite clear. Mention may be made here that Jampel et al. have earlier observed in their UV studies of a solution

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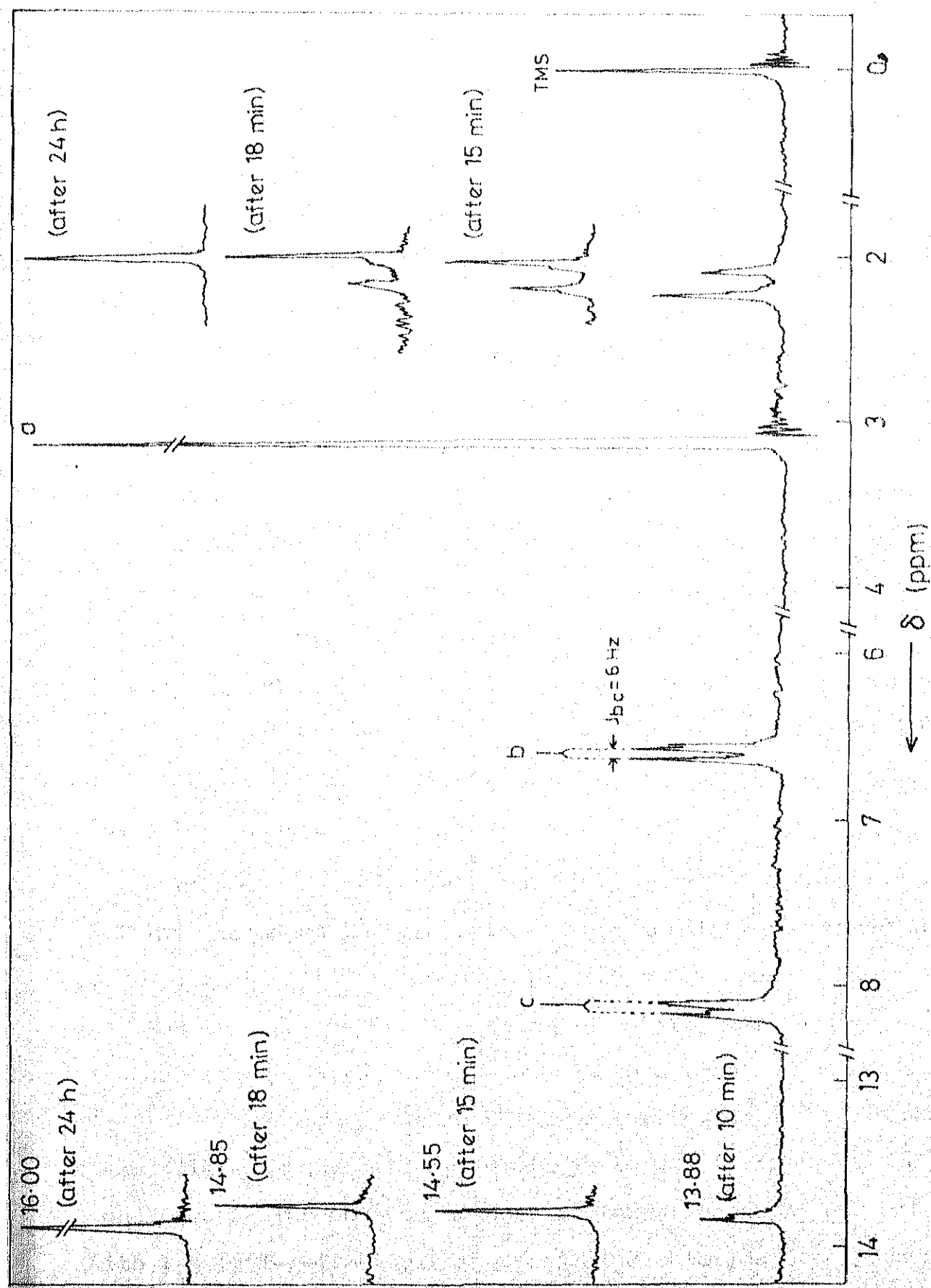


Fig. I-A-13 ^1H NMR spectrum (90 MHz) of **41a**.

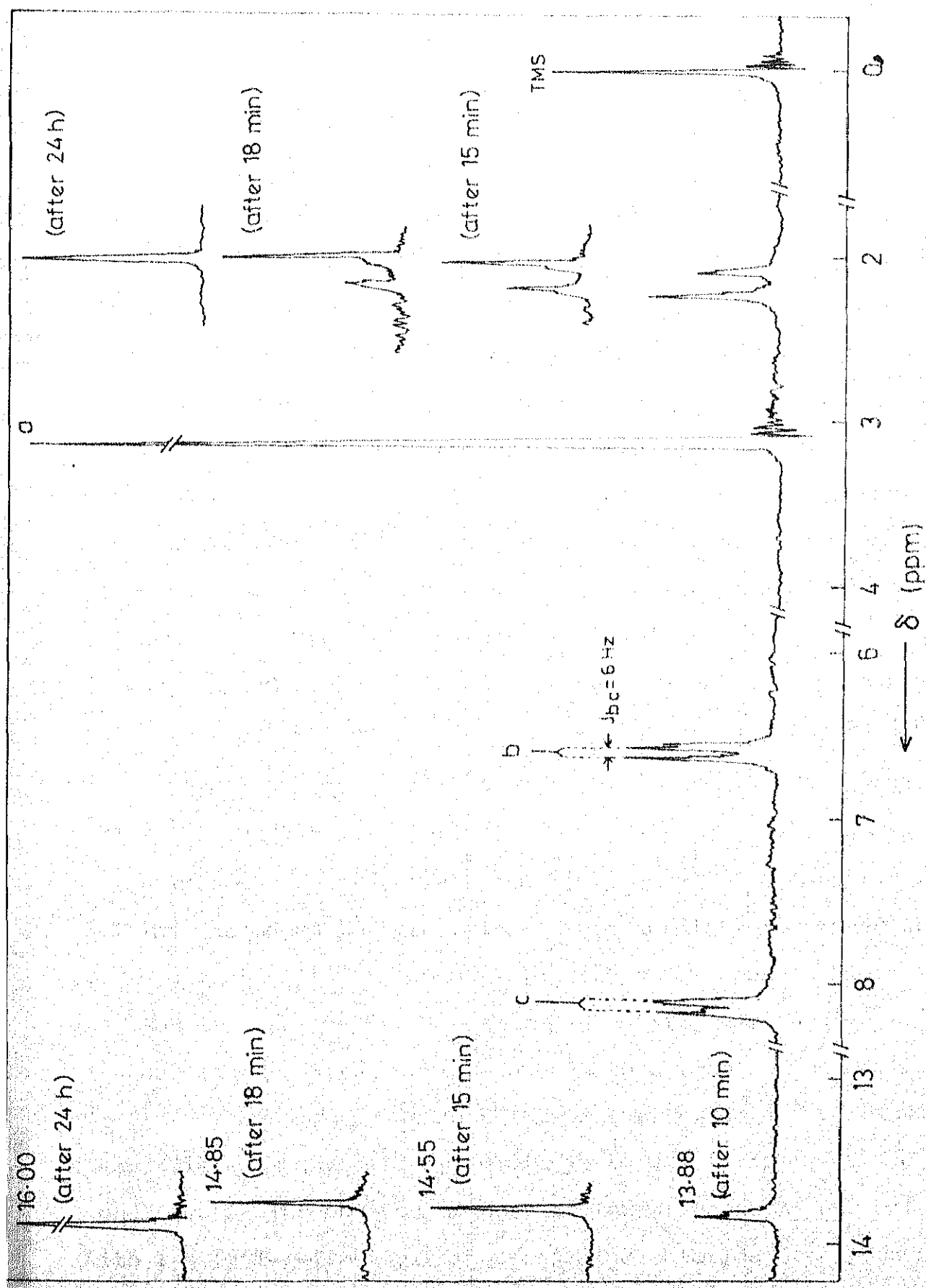


Fig. I-A-13 ^1H NMR spectrum (90 MHz) of **41a**.

of acetic anhydride and DMAP, that the absorption at 312 nm slowly decreases and a new peak appears at 282 nm, analogous to that of the 4-dimethylaminopyridinium acetate.⁸⁶ It may be pointed out here that the disappearance of the peak at 312 nm might be due to the decomposition of the 1-acetyl-4-dimethylaminopyridinium acetate (41) giving rise to ketene. The IR spectrum of 41a in chloroform showed absorptions at 3400, 1640 and 1600 cm^{-1} characteristic of the amide group. The IR spectrum recorded after a few hours showed a broad absorption between 3100-2500 cm^{-1} and a strong absorption at 1710 cm^{-1} characteristic of the acid group. The spectrum also showed an absorption at 1820 cm^{-1} characteristic of a four membered lactone (diketene) and one at 1910 cm^{-1} presumably due to the ketene. The appearance of the carbonyl absorption of an acid might be due to the formation of acetic acid by hydrolysis of ketene in the solution cell.

In order to trap the ketene formed from 41a in solution, aniline was added to a solution of 41a in dichloromethane which yielded acetanilide in good yield within six hours. Based on our PMR studies, we believe that aniline being quite reactive has reacted with the liberated ketene to give acetanilide. Tertiary alcohols, being much less reactive, do not react with 1-acetyl-4-dimethylaminopyridinium chloride (41a), under the same conditions. The absence of acetate formation from tert-butanol with 1-acetyl-4-dimethylaminopyridinium chloride (41a), tosylate

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In summary, the mechanistic pathway 'C' invoking the intermediacy of ketene and subsequent dimerization to diketene, in the reaction of 4-dimethylaminopyridine and acetic anhydride at high concentrations, seems more plausible, considering the following facts: i) The formation of cyclic carbonates and monoacetoacetates in the reaction of pinacols could be rationalized conveniently. ii) The formation of acetoacetates in the case of simple tertiary alcohols could be explained. iii) The formation of products apart from simple propionates could be understood in the reaction of propionic anhydride and DMAP. iv) Isolation of dehydroacetic acid could be accounted for. v) Finally, the PMR spectrum of 1-acetyl-4-dimethylaminopyridinium chloride could be explained satisfactorily.

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I.A.4 EXPERIMENTAL

General Procedures

All reactions were performed in oven-dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified. Distilled water is used for aqueous work-ups. Reaction product solutions were concentrated using a Perfit rotary evaporator.

Materials

Commercial grade solvents were distilled prior to use. Petroleum ether used was the fraction 60-80°C. Diethyl ether and tetrahydrofuran were distilled from lithium aluminium hydride; acetone was distilled from potassium permanganate; triethylamine was distilled from potassium hydroxide pellets. Methylene chloride, chloroform and carbon tetrachloride were distilled from phosphorous pentoxide. tert-Butyl alcohol and petroleum ether were distilled from sodium. Acetic anhydride was distilled from phosphorous pentoxide immediately before use. Dimethylaminopyridine (DMAP) was obtained from Aldrich Chemicals Co. (m.p. 108-110°C) and used without further purification.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60F-254 0.25 mm plates.

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Column chromatography was performed using 100-200 mesh Acme silica gel. The flash chromatography was performed using Acme thin-layer chromatography silica gel.

Physical Data

Melting points (m.p.) were determined with a uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Infrared (IR) spectra were recorded on Perkin-Elmer model 377 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 60 MHz on a Jeol PMX-60 instrument, at 80 MHz on a Bruker WP-80 instrument, at 90 MHz on a Varian EM-390 instrument and at 100 MHz on a Varian HA-100 and XL-100 instruments. Chemical shifts are reported in parts per million downfield from internal

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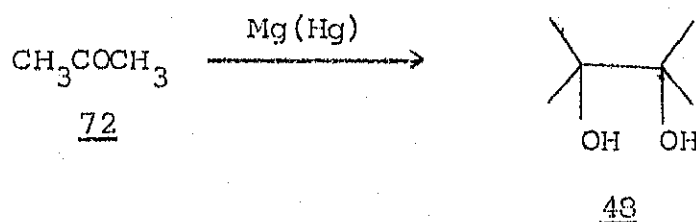
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reference tetramethylsilane (6). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), etc. Coupling constants are reported wherever necessary and are expressed in Hz.

Mass spectra (MS) were measured on a VG Micromass 7070F mass spectrometer. Principal molecular fragments are reported. Yields are reported based on the recovery of the starting material.

I.A.4.1 Preparation of Starting Materials

I.A.4.1a 2,3-Dihydroxy-2,3-dimethylbutane (48)



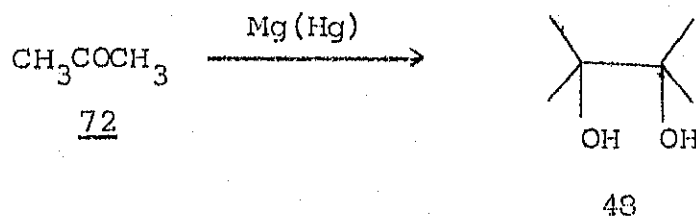
A solution of mercuric chloride (9.0 g, 33 mmol) in dry acetone (50 mL) was carefully added to magnesium turnings (8.0 g, 0.328 atoms) taken in dry benzene (80 mL). After the vigorous reaction stopped, a mixture of acetone (26 mL) and benzene (20 mL) was added to the reaction mixture. The resulting mixture was heated on a water bath for 2 h. The solid mass was broken and refluxed for an additional 1 h. Water was added (50 mL) and heated for 1 h. The reaction mixture was cooled to ca. 50°C and filtered. The residue was heated with benzene

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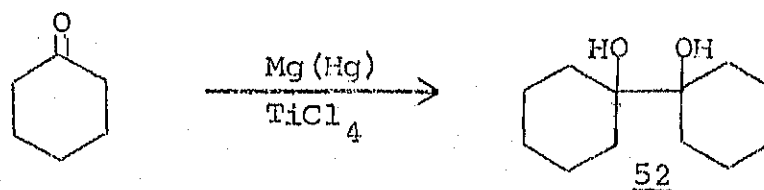


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(100 mL) for 10 minutes and filtered again. The combined filtrate was evaporated to half the volume. Water was added (70 mL) and cooled to 10–15°C. The separated pinacol hydrate was filtered, washed with benzene and air dried at room temperature to yield 35 g (47%, based on the magnesium used) of the pinacol hexahydrate; recrystallised from equal weight of boiling water, m.p. 46–46.5°C (lit.⁸⁷ m.p. 46–47°C).

The pinacol hydrate (20 g) was taken in dry benzene (150 mL) and refluxed, with the azeotropic removal of water by means of Dean-Stark water separator, until 10.4 mL of water was collected, to afford the anhydrous 48 as a colourless oil.

I.A.4.1b 1,1'-Dihydroxybicyclohexane (52)

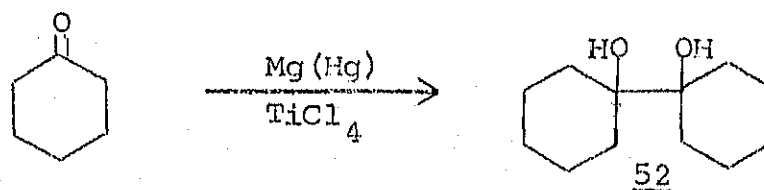


To a solution of mercuric chloride (0.44 g, 0.32 mmol) in tetrahydrofuran (6 mL) was added freshly cleaned magnesium (0.288 g, 12.0 mmol) and the resulting mixture was stirred at room temperature for 0.25 h. The turbid supernatant liquid was withdrawn by syringe and the amalgam was washed with three portions of tetrahydrofuran (5 mL). The mixture was cooled to ca. -10°C after adding tetrahydrofuran (60 mL) and treated dropwise with titanium tetrachloride (3.3 mL, 5.70 g, 30 mmol). A solution of cyclohexanone (1.96 g, 20 mmol) in tetrahydrofuran

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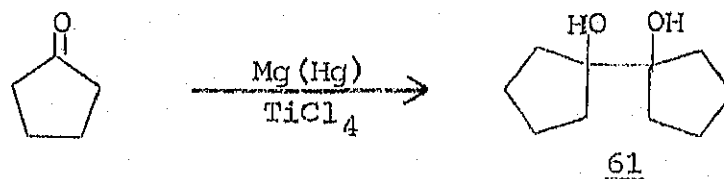
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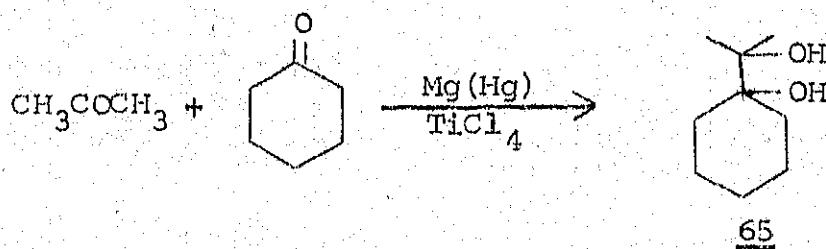
(50 mL) was added to the yellow green mixture and the resulting purple reaction mixture was stirred at ca. 0°C for 0.25 h. The reaction was quenched with saturated potassium carbonate solution (5 mL) and stirred at 0°C for 0.25 h. The dark blue mixture was diluted with ether and filtered through a pad of celite and sand. The filtrate was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated to afford 1.9 g of colourless crystals. Recrystallization from ether-petroleum ether gave 1.78 g (92%) of 52 as colourless crystals, m.p. 124-125°C (lit.⁶⁷ m.p. 124-125°C).

I.A.4.1c 1,1'-Dihydroxybicyclopentane (61)



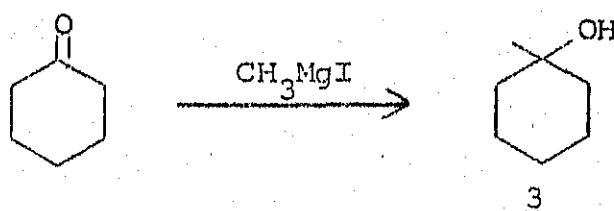
The reaction was carried out as described for cyclohexanone, with cyclopentanone (4.2 g, 50 mmol) to yield 3.42 g (90%) of colourless crystals of 61, m.p. 111.5 - 112°C (lit.⁶⁷ m.p. 111-112°C).

I.A.4.1d 1-(2'-hydroxypropyl)cyclohexanol (65)



The magnesium amalgam was prepared as in the earlier case with mercuric chloride (1.2 g, 4.42 mmol) and magnesium (3.84 g, 160 mmol). Tetrahydrofuran (60 mL) was added and the mixture was cooled to -10°C and treated dropwise with titanium tetrachloride (8.8 mL, 80 mmol). A solution of cyclohexanone (1.96 g, 20 mmol) and acetone (3.48 g, 60 mmol) in tetrahydrofuran (20 mL) was added. After stirring for 1.5 h at ca. 0°C , saturated aqueous potassium carbonate solution was added (3 mL) and stirred for 0.25 h at 0°C . The reaction mixture was diluted with ether and filtered through a pad of celite and sand. The filtrate was washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated to afford an oil which upon column chromatography over silica gel (elution with 1:4 ether-petroleum ether), yielded 2.30 g (75%) of 65 as colourless crystals, m.p. 82°C (lit.⁶⁷ m.p. $82-83^{\circ}\text{C}$).

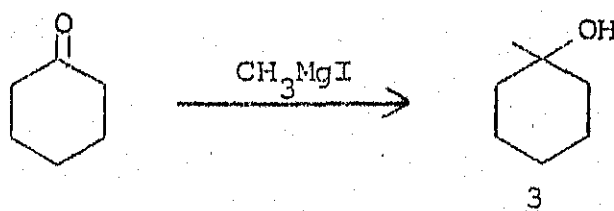
I.A.4.1c 1-Methylcyclohexanol (3)



A solution of distilled methyl iodide (8.52 g, 60 mmol) in anhydrous ether (20 mL) was added dropwise to magnesium turnings (1.44 g, 60 mmol) taken in dry ether (15 mL) containing a crystal of iodine, under nitrogen atmosphere. After the addition was over, the mixture was stirred for 0.25 h at room

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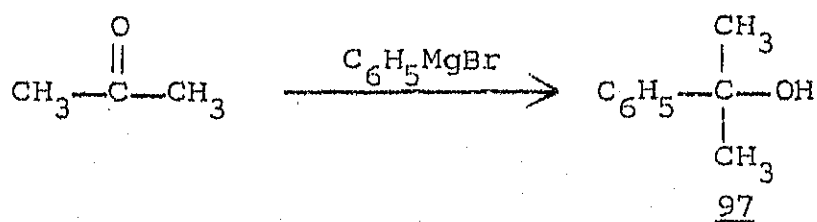
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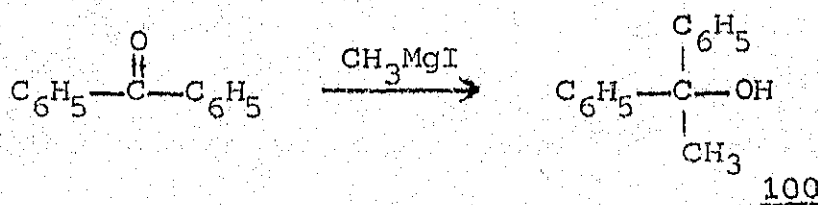
temperature. A solution of cyclohexanone (5.39 g, 55 mmol) in ether (20 mL) was added dropwise to the cold reaction mixture. The resulting mixture was stirred for 1 h and allowed to stand overnight. Saturated ammonium chloride solution was added to the cooled reaction mixture and extracted with ether (4 x 30 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated. The crude product upon distillation yielded 5.64 g (90%) of an oil, b.p. 55-56°C (10 mm) [lit.⁸⁸ b.p. 54-56°C (10 mm)].

1.A.4.1f 2-Phenylpropan-2-ol (97)



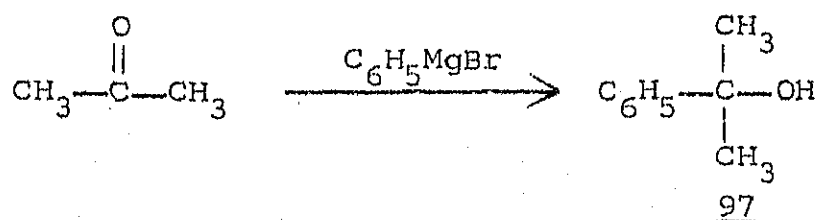
The Grignard reaction was performed as in the earlier case with phenyl magnesium bromide prepared from phenyl bromide (15.7 g, 100 mmol) and magnesium (2.4 g, 100 mmol) in dry ether and dry acetone (5.8 g, 100 mmol). The reaction after the work-up yielded 10.9 g (88%) of 97, b.p. 87-89°C (9 mm) [lit.⁸⁹ b.p.⁸⁹ 87-90°C (9 mm)].

I.A.4.1g 1,1-Diphenylethanol (100)



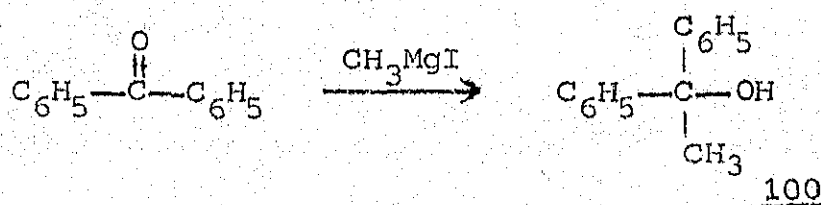
temperature. A solution of cyclohexanone (5.39 g, 55 mmol) in ether (20 mL) was added dropwise to the cold reaction mixture. The resulting mixture was stirred for 1 h and allowed to stand overnight. Saturated ammonium chloride solution was added to the cooled reaction mixture and extracted with ether (4 x 30 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated. The crude product upon distillation yielded 5.64 g (90%) of an oil, b.p. 55-56°C (10 mm) [lit.⁸⁸ b.p. 54-56°C (10 mm)].

1.A.4.1f 2-Phenylpropan-2-ol (97)



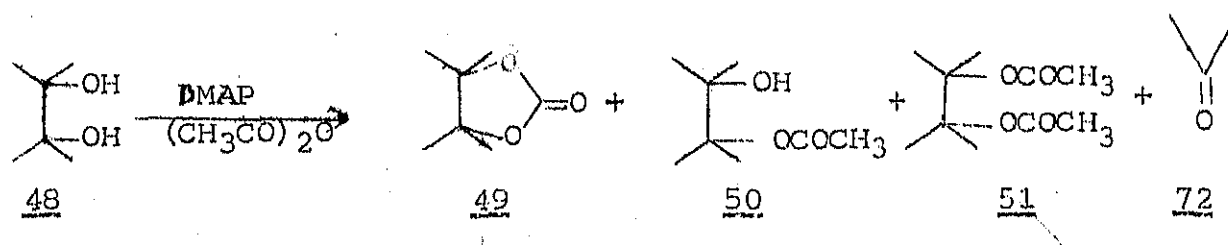
The Grignard reaction was performed as in the earlier case with phenyl magnesium bromide prepared from phenyl bromide (15.7 g, 100 mmol) and magnesium (2.4 g, 100 mmol) in dry ether and dry acetone (5.8 g, 100 mmol). The reaction after the work-up yielded 10.9 g (88%) of 97, b.p. 87-89°C (9 mm) [lit.⁸⁹ b.p.⁸⁹ 87-90°C (9 mm)].

I.A.4.1g 1,1-Diphenylethanol (100)



The Grignard reaction was carried out as above with methyl magnesium iodide (100 mmol) prepared from methyl iodide and magnesium and benzophenone (18.2 g, 10 mmol) in dry ether to yield 15.84 g (80%) of 100 as colourless crystals, recrystallised from petroleum ether, m.p. 78-79°C (lit.⁸⁹ m.p. 81°C).

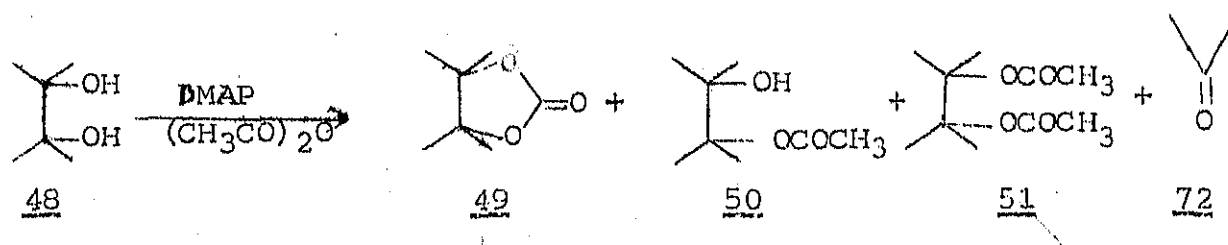
I.A.4.2 Reaction of Pinacol 48 with Acetic anhydride and 4-Dimethylaminopyridine



To a mixture of acetic anhydride (0.45 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol) was added 48 (0.236 g, 2 mmol). The reaction mixture was heated with stirring at ca. 85°C for 3 h. The reaction was quenched by adding a few drops of methanol followed by water (10 mL). After stirring the reaction mixture for ten minutes, it was extracted with dichloromethane (3x20 mL). The organic layer was washed with water (10 mL) followed by brine (10 mL) and then dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure to afford a brown oil which was chromatographed over silica gel to give 0.05 g of 51 (17%, elution with petroleum ether), m.p. 64-65°C (lit.⁶⁶ m.p. 65°C), 0.06 g of 50 (26%, elution with 1:1 ether-petroleum ether) as a pale yellow oil, 0.11 g of 49 (51%,

The Grignard reaction was carried out as above with methyl magnesium iodide (100 mmol) prepared from methyl iodide and magnesium and benzophenone (18.2 g, 10 mmol) in dry ether to yield 15.84 g (80%) of 100 as colourless crystals, recrystallised from petroleum ether, m.p. 78-79°C (lit.⁸⁹ m.p. 81°C).

I.A.4.2 Reaction of Pinacol 48 with Acetic anhydride and 4-Dimethylaminopyridine



To a mixture of acetic anhydride (0.45 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol) was added 48 (0.236 g, 2 mmol). The reaction mixture was heated with stirring at ca. 85°C for 3 h. The reaction was quenched by adding a few drops of methanol followed by water (10 mL). After stirring the reaction mixture for ten minutes, it was extracted with dichloromethane (3x20 mL). The organic layer was washed with water (10 mL) followed by brine (10 mL) and then dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure to afford a brown oil which was chromatographed over silica gel to give 0.05 g of 51 (17%, elution with petroleum ether), m.p. 64-65°C (lit.⁶⁶ m.p. 65°C), 0.06 g of 50 (26%, elution with 1:1 ether-petroleum ether) as a pale yellow oil, 0.11 g of 49 (51%,

elution with 1:9 ether-petroleum ether), m.p. 179-180°C (lit.⁶⁵ m.p. 180-181°C) and 0.06 g of unreacted starting material 48 (elution with 1:5, ether-petroleum ether).

2,3-Diacetoxy-2,3-dimethylbutane (51)

IR (CHCl_3): 1730 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.3 (s, 12H, $-\text{CH}_3$); 2.0 (s, 6H, $-\text{CH}_3$).

2-Acetoxy-3-hydroxy-2,3-dimethylbutane (50)

IR (CCl_4): 3470 ($\nu_{\text{O-H}}$) and 1735 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.3 (s, 6H, $-\text{CH}_3$); 1.4 (s, 6H, $-\text{CH}_3$); 1.95 (s, 3H, $-\text{CH}_3$) and 3.26 (s, 1H, $-\text{OH}$, D_2O exchangeable).

MS (m/e): 145 ($\text{M}^+ - \text{CH}_3$), 143, 116, 101, 85, 83, 69, 59, 43.

2-Oxo-4,4,5,5-Tetramethyl-1,3-dioxolane (49)

IR (CCl_4): 1790 ($\nu_{\text{O-C=O}}$).

PMR (CDCl_3): 1.3 (s).

In a repeat reaction, a condenser with ice water circulation was set downwards for distillation with a receiver containing 2,4-dinitrophenylhydrazene solution in methanol, cooled in ice-salt freezing mixture. An orange yellow precipitate was separated in the receiver, which was filtered, washed with cold methanol and dried. The orange compound identified as

elution with 1:9 ether-petroleum ether), m.p. 179-180°C (lit.⁶⁵ m.p. 180-181°C) and 0.06 g of unreacted starting material 48 (elution with 1:5, ether-petroleum ether).

2,3-Diacetoxy-2,3-dimethylbutane (51)

IR (CHCl_3): 1730 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.3 (s, 12H, $-\text{CH}_3$); 2.0 (s, 6H, $-\text{CH}_3$).

2-Acetoxy-3-hydroxy-2,3-dimethylbutane (50)

IR (CCl_4): 3470 ($\nu_{\text{O-H}}$) and 1735 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.3 (s, 6H, $-\text{CH}_3$); 1.4 (s, 6H, $-\text{CH}_3$); 1.95 (s, 3H, $-\text{CH}_3$) and 3.26 (s, 1H, $-\text{OH}$, D_2O exchangeable).

MS (m/e): 145 ($\text{M}^+ - \text{CH}_3$), 143, 116, 101, 85, 83, 69, 59, 43.

2-Oxo-4,4,5,5-Tetramethyl-1,3-dioxolane (49)

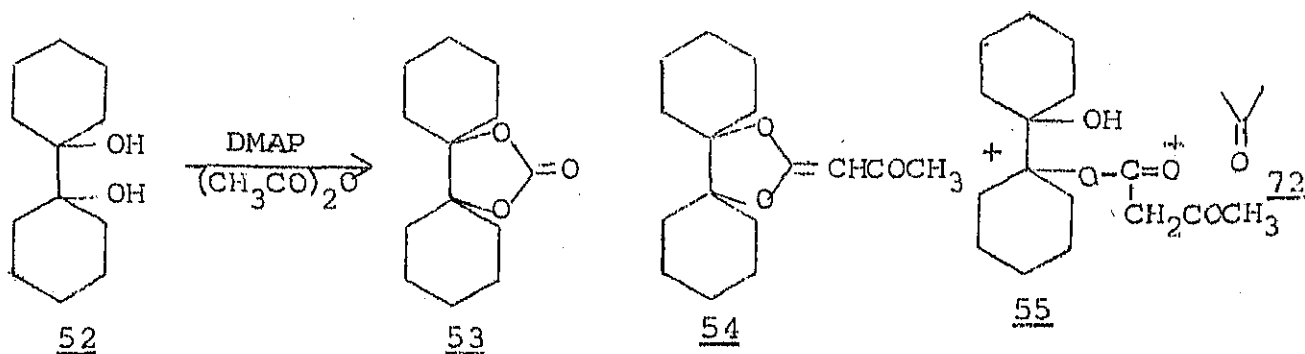
IR (CCl_4): 1790 ($\nu_{\text{O=C-O}}$).

PMR (CDCl_3): 1.3 (s).

In a repeat reaction, a condenser with ice water circulation was set downwards for distillation with a receiver containing 2,4-dinitrophenylhydrazene solution in methanol, cooled in ice-salt freezing mixture. An orange yellow precipitate was separated in the receiver, which was filtered, washed with cold methanol and dried. The orange compound identified as

2,4-dinitrophenylhydrazone of acetone was recrystallised from aqueous ethanol, m.p. 127-128°C (lit.⁶⁵ m.p. 126-127°C).

I.A.4.3 Reaction of Pinacol 52 with Acetic anhydride and 4-Dimethylaminopyridine



The reaction was carried out as above with pinacol 52 (0.792 g, 4 mmol), acetic anhydride (0.88 g, 8.8 mmol) and DMAP (0.488 g, 4 mmol). A brown oily solid was obtained after the work-up, which was chromatographed over silica gel using medium pressure liquid chromatography (MPLC), to give the following products. Elution with 1:9 ether petroleum ether gave 0.05 g of 54 (15%), 0.07 g of 53 (21%), m.p. 178-179°C, 0.07 g of 55 (17%) and 0.5 g of recovered starting material.

2-Acetonilidene-4,5-bis(cyclohexyl)-1,3-dioxolane (54)

IR (CCl₄): 1680 ($\nu_{\text{C=O}}$) and 1640 ($\nu_{\text{C=C}}$).

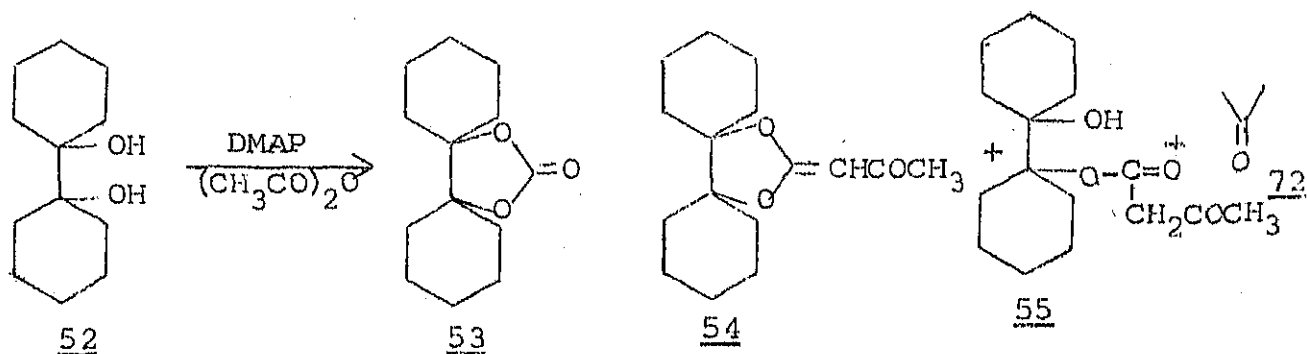
PMR (CDCl₃): 1-2 (m, 20 H, -CH₂), 2.26 (s, 3H, -CH₃), 4.8 (s, 1H, vinylic).

MS (m/e): 264 (M⁺), 249, 163, 121, 95, 81, 67.

Exact Mass: Calcd for C₁₆H₂₄O₃: 264.1726. Found: 264.1720.

2,4-dinitrophenylhydrazone of acetone was recrystallised from aqueous ethanol, m.p. 127-128°C (lit.⁶⁵ m.p. 126-127°C).

I.A.4.3 Reaction of Pinacol 52 with Acetic anhydride and 4-Dimethylaminopyridine



The reaction was carried out as above with pinacol 52 (0.792 g, 4 mmol), acetic anhydride (0.88 g, 8.8 mmol) and DMAP (0.488 g, 4 mmol). A brown oily solid was obtained after the work-up, which was chromatographed over silica gel using medium pressure liquid chromatography (MPLC), to give the following products. Elution with 1:9 ether petroleum ether gave 0.05 g of 54 (15%), 0.07 g of 53 (21%), m.p. 178-179°C, 0.07 g of 55 (17%) and 0.5 g of recovered starting material.

2-Acetylidene-4,5-bis(cyclohexyl)-1,3-dioxolane (54)

IR (CCl_4): 1680 ($\nu_{\text{C=O}}$) and 1640 ($\nu_{\text{C=C}}$).

PMR (CDCl_3): 1-2 (m, 20 H, $-\text{CH}_2-$), 2.26 (s, 3H, $-\text{CH}_3$), 4.8 (s, 1H, vinylic).

MS (m/e): 264 (M^+), 249, 163, 121, 95, 81, 67.

Exact Mass: Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_3$: 264.1726. Found: 264.1720.

2-Oxo-4,5-bis(cyclohexyl)-1,3-dioxolane (53)

IR (KBr): 1780 ($\nu_{\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{O}$).

PMR (CDCl_3): 1.0 - 2.2 (br, m, $-\overset{1}{\text{CH}_2}$).

MS (m/e): 224 (M^+), 180, 137, 110, 99, 98, 82, 81, 70, 69, 67.

Exact Mass: Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3$: 224.1416. Found: 224.1418.

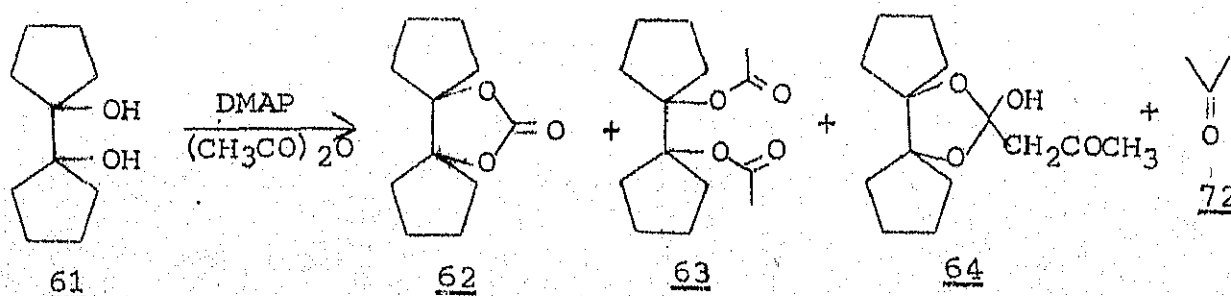
1-Acetoacetoxy-1'-hydroxy-1,1'-bicyclohexane (55)

IR (thin film): 3440 ($\nu_{\text{O}-\text{H}}$), 1730 ($\nu_{\text{C}=\text{O}}$) and 1700 ($\nu_{\text{C}=\text{O}}$).

PMR (CDCl_3): 1.0 - 1.89 (m, 20 H, $-\overset{1}{\text{CH}_2}$); 2.25 (s, 3H, $-\text{CH}_3$); 3.5 (s, 2H, $-\overset{1}{\text{CH}_2}$); 4.18 (s, 1H, $-\text{OH}$, D_2O exchangeable).

MS (m/e): 264 (M^+-18), 249, 242, 180, 163, 137, 100, 99, 98, 86, 84.

Exact Mass: Calcd for $\text{C}_{16}\text{H}_{26}\text{O}_4$ (M-18): 264.1726. Found: 264.1717.

I.A.4.4 Reaction of Pinacol 61 with Acetic anhydride and 4-Dimethylaminopyridine

2-Oxo-4,5-bis(cyclohexyl)-1,3-dioxolane (53)

IR (KBr): 1780 ($\nu_{\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{O}$).

PMR (CDCl_3): 1.0 - 2.2 (br, m, $-\overset{1}{\text{CH}_2}$).

MS (m/e): 224 (M^+), 180, 137, 110, 99, 98, 82, 81, 70, 69, 67.

Exact Mass: Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3$: 224.1416. Found: 224.1418.

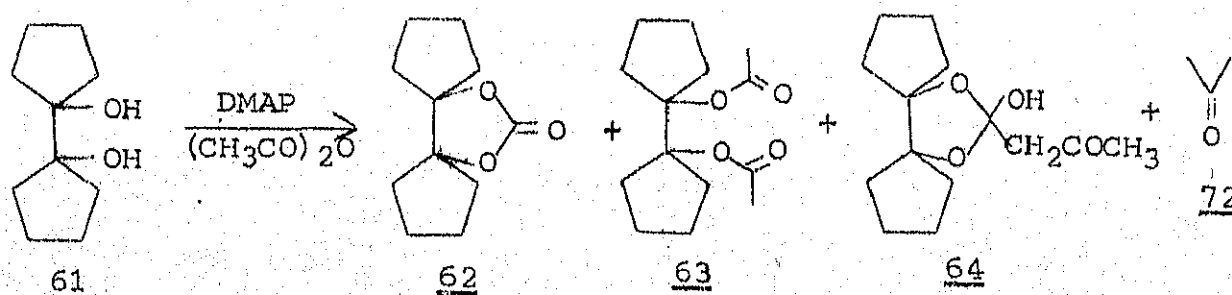
1-Acetoacetoxy-1'-hydroxy-1,1'-bicyclohexane (55)

IR (thin film): 3440 ($\nu_{\text{O}-\text{H}}$), 1730 ($\nu_{\text{C}=\text{O}}$) and 1700 ($\nu_{\text{C}=\text{O}}$).

PMR (CDCl_3): 1.0 - 1.89 (m, 20 H, $-\overset{1}{\text{CH}_2}$); 2.25 (s, 3H, $-\text{CH}_3$); 3.5 (s, 2H, $-\overset{1}{\text{CH}_2}$); 4.18 (s, 1H, $-\text{OH}$, D_2O exchangeable).

MS (m/e): 264 (M^+-18), 249, 242, 180, 163, 137, 100, 99, 98, 86, 84.

Exact Mass: Calcd for $\text{C}_{16}\text{H}_{26}\text{O}_4$ (M-18): 264.1726. Found: 264.1717.

I.A.4.4 Reaction of Pinacol 61 with Acetic anhydride and 4-Dimethylaminopyridine

Reaction was carried out under identical conditions with pinacol 61 (0.34 g, 2 mmol), acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol) for 4 h. The brown oil obtained after the work-up was purified by flash column chromatography to yield 0.1 g of 63 (32%, elution with petroleum ether), 0.05 g of 64 (16%, elution with 1:19 ether-petroleum ether), 0.06 g of 62, m.p. 89-90°C (24%, elution with 1:19 ether-petroleum ether) and 0.12 g of the starting material (elution with 3:17 ether-petroleum ether).

1,1'-Diacetoxy-1,1'-bicyclopentane (63)

IR (CCl₄): 1730 (ν $\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{O} \end{array}$).

PMR (CDCl₃): 1.25 - 2.0 (m, 16H, -CH_2); 2.04 (s, 6H, -CH_3).

2-Acetyl-2-hydroxy-4,5-bis(cyclopentyl)-1,3-dioxolane (64)

IR (thin film): 3415 ($\nu_{\text{O-H}}$), 1735 (ν $\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{O} \end{array}$) and 1705 ($\nu_{\text{C=O}}$).

PMR (CDCl₃): 1.4 - 2.0 (m, 16H, -CH_2); 2.08 (s, 5H, CH_3 , -CH_2); 4.33 (s, 1H, -OH , D₂O exchangeable).

MS (m/e): 254 (M⁺), 239, 195, 153, 152, 142, 135, 123, 111, 95, 85, 67.

2-Oxo-4,5-bis(cyclopentyl)-1,3-dioxolane (62)

IR (KBr): 1780 (ν $\begin{array}{c} \text{O} \\ \parallel \\ \text{-O-C-O-} \end{array}$).

PMR (CDCl₃): 1.6 - 2.2 (m, -CH_2).

Reaction was carried out under identical conditions with pinacol 61 (0.34 g, 2 mmol), acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol) for 4 h. The brown oil obtained after the work-up was purified by flash column chromatography to yield 0.1 g of 63 (32%, elution with petroleum ether), 0.05 g of 64 (16%, elution with 1:19 ether-petroleum ether), 0.06 g of 62, m.p. 89-90°C (24%, elution with 1:19 ether-petroleum ether) and 0.12 g of the starting material (elution with 3:17 ether-petroleum ether).

1,1'-Diacetoxy-1,1'-bicyclopentane (63)

IR (CCl₄): 1730 (ν $\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{O} \end{array}$).

PMR (CDCl₃): 1.25 - 2.0 (m, 16H, -CH_2); 2.04 (s, 6H, -CH_3).

2-Acetyl-2-hydroxy-4,5-bis(cyclopentyl)-1,3-dioxolane (64)

IR (thin film): 3415 ($\nu_{\text{O-H}}$), 1735 (ν $\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{O} \end{array}$) and 1705 ($\nu_{\text{C=O}}$).

PMR (CDCl₃): 1.4 - 2.0 (m, 16H, -CH_2); 2.08 (s, 5H, CH_3 , -CH_2); 4.33 (s, 1H, -OH , D₂O exchangeable).

MS (m/e): 254 (M⁺), 239, 195, 153, 152, 142, 135, 123, 111, 95, 85, 67.

2-Oxo-4,5-bis(cyclopentyl)-1,3-dioxolane (62)

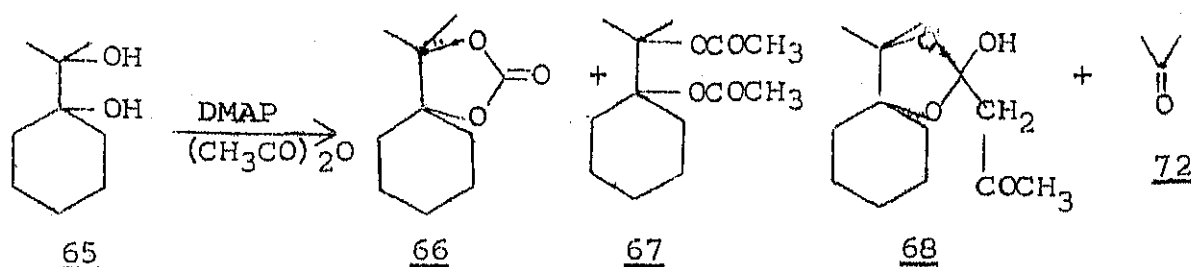
IR (KBr): 1780 (ν $\begin{array}{c} \text{O} \\ \parallel \\ \text{-O-C-O} \end{array}$).

PMR (CDCl₃): 1.6 - 2.2 (m, -CH_2).

MS (m/e): 196 (M^+), 152, 124, 111, 108, 97, 95, 84, 67, 53.

Exact Mass: Calcd for $C_{11}H_{16}O_3$: 196.1100. Found: 196.1106.

I.A.4.5 Reaction of Pinacol 65 with Acetic anhydride and 4-Dimethylaminopyridine



The pinacol 65 (0.316 g, 2 mmol) was treated with acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol) under identical conditions as above, to obtain a brown oil. The crude product mixture was subjected to flash chromatography to yield 0.06 g of 67 (17%, elution with 1:19 ether-petroleum ether), 0.09 g of 66, m.p. 112-112.5°C (34%, elution with 1:9 ether-petroleum ether), 0.1 g of 68 (28%, elution with 1:9 ether-petroleum ether) and 0.085 g of recovered pinacol (elution with 3:17 ether-petroleum ether).

1-(2'-Acetoxypropyl)cyclohexylacetate (67)

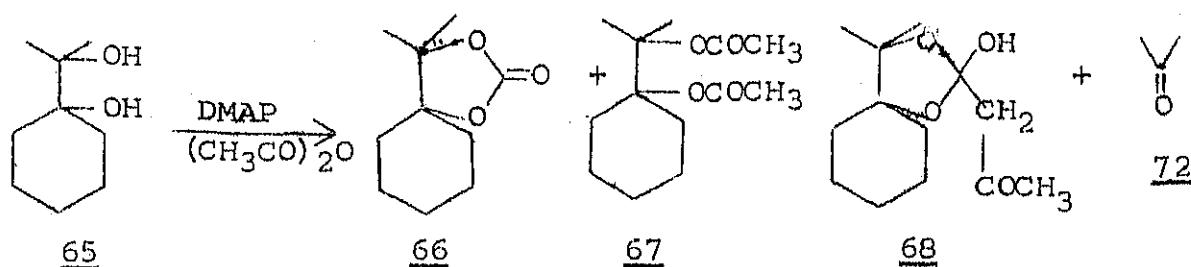
IR (thin film): 1735 ($\nu_{C=O}$).

PMR ($CDCl_3$): 1.09 (s, 6H, $-CH_3$); 1.16-1.43 (m, 10 H, $-CH_2-$); 1.53 (s, 6H, $-CH_3$).

MS (m/e): 196 (M^+), 152, 124, 111, 108, 97, 95, 84, 67, 53.

Exact Mass: Calcd for $C_{11}H_{16}O_3$: 196.1100. Found: 196.1106.

I.A.4.5 Reaction of Pinacol 65 with Acetic anhydride and 4-Dimethylaminopyridine



The pinacol 65 (0.316 g, 2 mmol) was treated with acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol) under identical conditions as above, to obtain a brown oil. The crude product mixture was subjected to flash chromatography to yield 0.06 g of 67 (17%, elution with 1:19 ether-petroleum ether), 0.09 g of 66, m.p. 112-112.5°C (34%, elution with 1:9 ether-petroleum ether), 0.1 g of 68 (28%, elution with 1:9 ether-petroleum ether) and 0.085 g of recovered pinacol (elution with 3:17 ether-petroleum ether).

1-(2'-Acetoxypropyl)cyclohexylacetate (67)

IR (thin film): 1735 ($\nu_{C=O}$).

PMR ($CDCl_3$): 1.09 (s, 6H, $-CH_3$); 1.16-1.43 (m, 10 H, $-CH_2-$); 1.53 (s, 6H, $-CH_3$).

MS (m/e): 182 ($M^+ - CH_3COOH$), 157, 140, 125, 122, 107, 99, 97, 72, 70.

2-Oxo-4-cyclohexyl-5,5-dimethyl-1,3-dioxolane (66)

IR (KBr) : 1780 ($\nu_{O-\overset{O}{\parallel}C-O}$).

PMR ($CDCl_3$): 1.36 (s, 6H, $-CH_3$); 1.44 - 2.04 (m, 10 H, $-CH_2$).

MS (m/e): 184 (M^+), 140, 125, 122, 90, 98, 97, 85, 81, 70, 67, 59, 55.

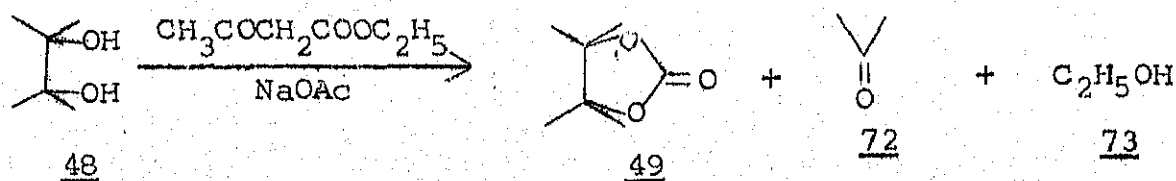
Exact Mass: Calcd for $C_{10}H_{16}O_3$: 184.1100. Found: 184.1096.

2-Acetyl-2-hydroxy-4-cyclohexyl-5,5-dimethyl-1,3-dioxolane (68)

IR (thin film): 3440 cm^{-1} (ν_{O-H}), 1735 ($\nu_{\overset{O}{\parallel}C-O}$), 1710 ($\nu_{C=O}$).

PMR ($CDCl_3$): 1.13 - 1.66 (m, 10 H, $-CH_2$); 1.53 (s, 6H, $-CH_3$); 2.01 (s, 3H, $-CH_3$); 2.23 (s, 2H, $-CH_2$), 2.92 (s, 1H, $-OH$, D_2O exchangeable).

I.A.4.6 Reaction of Pinacol 48 with Ethylacetoacetate



A mixture of pinacol 48 (1.13 g, 5 mmol), ethylacetoacetate (0.65 g, 5 mmol) and anhydrous sodium acetate is heated at

MS (m/e): 182 ($M^+ - CH_3COOH$), 157, 140, 125, 122, 107, 99, 97, 72, 70.

2-Oxo-4-cyclohexyl-5,5-dimethyl-1,3-dioxolane (66)

IR (KBr) : 1780 ($\nu_{O-\overset{\overset{O}{\parallel}}{C}-O}$).

PMR ($CDCl_3$): 1.36 (s, 6H, $-CH_3$); 1.44 - 2.04 (m, 10 H, $-CH_2$).

MS (m/e): 184 (M^+), 140, 125, 122, 90, 98, 97, 85, 81, 70, 67, 59, 55.

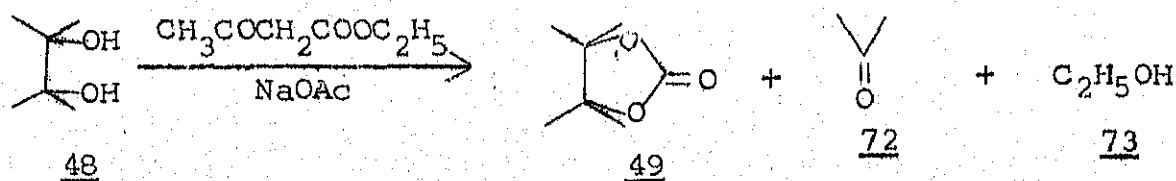
Exact Mass: Calcd for $C_{10}H_{16}O_3$: 184.1100. Found: 184.1096.

2-Acetyl-2-hydroxy-4-cyclohexyl-5,5-dimethyl-1,3-dioxolane (68)

IR (thin film): 3440 cm^{-1} (ν_{O-H}), 1735 ($\nu_{\overset{\overset{O}{\parallel}}{C}-O}$), 1710 ($\nu_{C=O}$).

PMR ($CDCl_3$): 1.13 - 1.66 (m, 10 H, $-CH_2$); 1.53 (s, 6H, $-CH_3$); 2.01 (s, 3H, $-CH_3$); 2.23 (s, 2H, $-CH_2$), 2.92 (s, 1H, $-OH$, D_2O exchangeable).

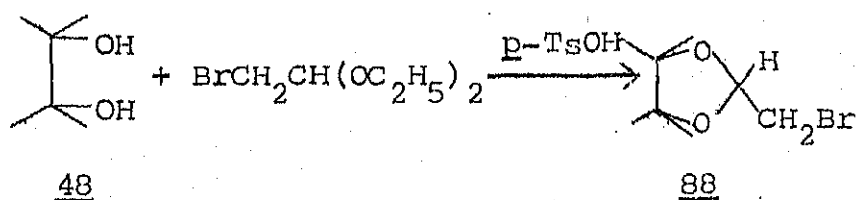
I.A.4.6 Reaction of Pinacol 48 with Ethylacetoacetate



A mixture of pinacol 48 (1.13 g, 5 mmol), ethylacetoacetate (0.65 g, 5 mmol) and anhydrous sodium acetate is heated at

ca. 140°C for 8 h with a condenser set downwards for distillation and a receiver containing a solution of 2,4-dinitrophenylhydrazene in methanol. An orange yellow precipitate separated in the receiver which was filtered, m.p. 127-128°C (lit.⁶⁵ m.p. 126-127°C). Water was added to the reaction mixture and extracted with ether. The ether extract was dried over anhydrous sodium sulphate, filtered and concentrated. Trituration of the residue with ether-petroleum ether (1:1) gave 0.36 g of 49 (50%), m.p. 179-180°C (lit.⁶⁵ m.p. 180-181°C).

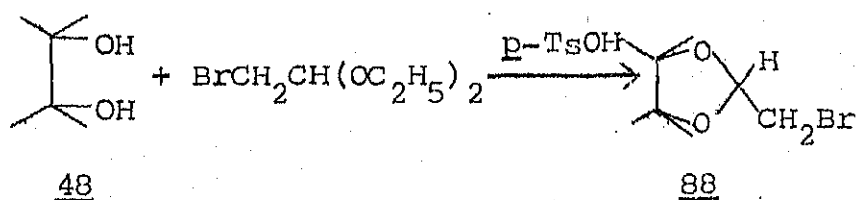
I.A.4.7a Preparation of 2-Bromomethyl-4,4,5,5-tetramethyl-1,3-dioxolane (88)



A mixture of bromoacetaldehyde diethylacetal⁷⁷ (6.8 g, 30.5 mmol) and anhydrous acetone pinacol (3.6 g, 30.5 mmol) is heated to 100°C in the presence of a catalytic amount of p-toluenesulphonic acid (50 mg). The ethanol formed was continuously removed using a Dean-Stark water separator (ca. 1.7 mL). The reaction mixture was diluted with ether and washed with saturated sodium bicarbonate solution (20 mL). The ether extract was dried over anhydrous magnesium sulphate and the solvent was evaporated under reduced pressure. The crude product was

ca. 140°C for 8 h with a condenser set downwards for distillation and a receiver containing a solution of 2,4-dinitrophenylhydrazene in methanol. An orange yellow precipitate separated in the receiver which was filtered, m.p. 127-128°C (lit.⁶⁵ m.p. 126-127°C). Water was added to the reaction mixture and extracted with ether. The ether extract was dried over anhydrous sodium sulphate, filtered and concentrated. Trituration of the residue with ether-petroleum ether (1:1) gave 0.36 g of 49 (50%), m.p. 179-180°C (lit.⁶⁵ m.p. 180-181°C).

I.A.4.7a Preparation of 2-Bromomethyl-4,4,5,5-tetramethyl-1,3-dioxolane (88)

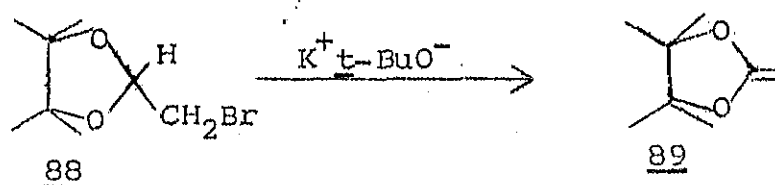


A mixture of bromoacetaldehyde diethylacetal⁷⁷ (6.8 g, 30.5 mmol) and anhydrous acetone pinacol (3.6 g, 30.5 mmol) is heated to 100°C in the presence of a catalytic amount of p-toluenesulphonic acid (50 mg). The ethanol formed was continuously removed using a Dean-Stark water separator (ca. 1.7 mL). The reaction mixture was diluted with ether and washed with saturated sodium bicarbonate solution (20 mL). The ether extract was dried over anhydrous magnesium sulphate and the solvent was evaporated under reduced pressure. The crude product was

vacuum distilled to yield 4.76 g of 88 (70%) as a colourless liquid, b.p. 92-94°C (11 mm).

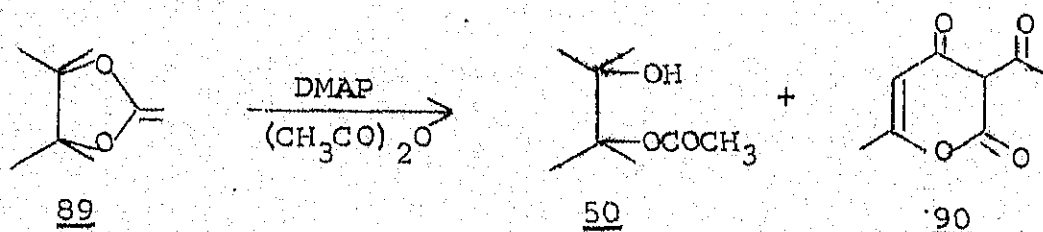
PMR (CDCl_3): 1.37 (s, 12H, CH_3); 3.34 (d, 2H, CH_2 , $J = 6$ Hz); 5.28 (t, 1H, CH, $J = 6$ Hz).

I.A.4.7b Preparation of 2-Methylene-4,4,5,5-tetramethyl-1,3-dioxolane (89)^{75,76}



A mixture of potassium metal (0.78 g, 20 mmol) and absolute tert-butanol (16 mL) was refluxed until all the potassium dissolved (ca. 2 h). After cooling the solution slightly, bromoacetal 88 (4.46 g, 20 mmol) was added quickly along with a few boiling chips. A cream coloured precipitate of potassium bromide started depositing immediately. The tert-butanol was distilled off under reduced pressure (200 mm). The ketene cyclic acetal 89 was collected in a receiver prewashed with alcoholic potassium hydroxide solution (1.84 g, 65%), b.p. 106°C (140 mm).

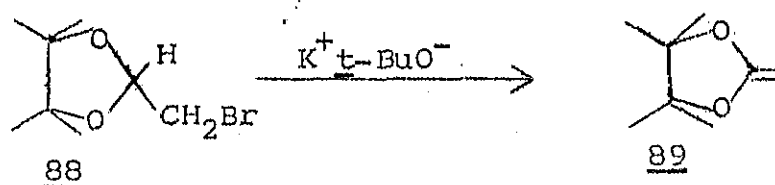
I.A.4.7c Reaction of Ketene Cyclic Acetal 89 with Acetic anhydride and 4-Dimethylaminopyridine



vacuum distilled to yield 4.76 g of 88 (70%) as a colourless liquid, b.p. 92-94°C (11 mm).

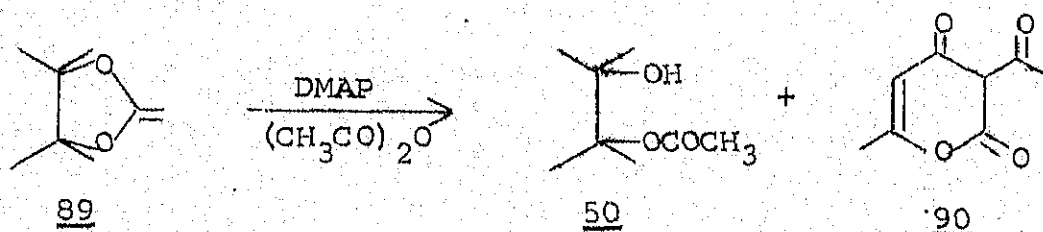
PMR (CDCl_3): 1.37 (s, 12H, CH_3); 3.34 (d, 2H, CH_2 , $J = 6$ Hz); 5.28 (t, 1H, CH, $J = 6$ Hz).

I.A.4.7b Preparation of 2-Methylene-4,4,5,5-tetramethyl-1,3-dioxolane (89)^{75,76}



A mixture of potassium metal (0.78 g, 20 mmol) and absolute tert-butanol (16 mL) was refluxed until all the potassium dissolved (ca. 2 h). After cooling the solution slightly, bromoacetal 88 (4.46 g, 20 mmol) was added quickly along with a few boiling chips. A cream coloured precipitate of potassium bromide started depositing immediately. The tert-butanol was distilled off under reduced pressure (200 mm). The ketene cyclic acetal 89 was collected in a receiver prewashed with alcoholic potassium hydroxide solution (1.84 g, 65%), b.p. 106°C (140 mm).

I.A.4.7c Reaction of Ketene Cyclic Acetal 89 with Acetic anhydride and 4-Dimethylaminopyridine



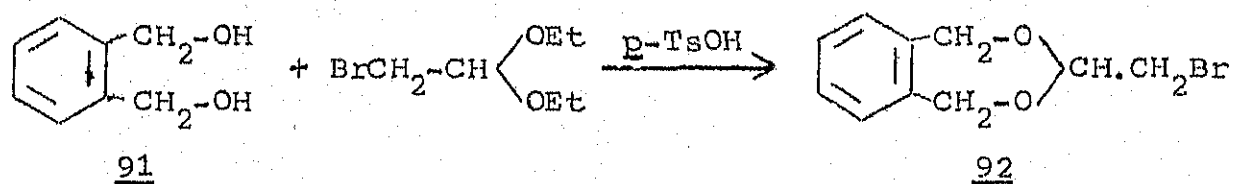
To a mixture of acetic anhydride (0.408 g, 4 mmol) and DMAP (0.244 g, 2 mmol) was added the ketene cyclic acetal 89 (0.568 g, 4 mmol). Heated the reaction mixture to 80-90°C with stirring for 2 h. Water (0.07 mL) was added and the heating was continued for two more hours. The crude product obtained after the usual work-up was purified by flash chromatography to yield 0.1 g of 50 (15%, elution with 5% ether-petroleum ether), 0.07 g of 90, m.p. 111-112°C (mixture m.p. with dehydroacetic acid, 111-112°C, elution with 1:19 ether-petroleum ether).

Dehydroacetic acid (90)

PMR (CDCl₃): 2.25 (s, 3H, -CH₃); 2.63 (s, 4H, CH₃, CH); 5.96 (s, 1H, vinylic).

MS (m/e): 168 (M⁺), 153, 125, 111, 98, 85, 69.

I.A.4.8a Preparation of 3-Bromomethyl-1,5-dihydro-2,4-benzodioxepin (92)



A mixture of phthalyl alcohol (91, 10 g, 72.5 mmol) and bromoacetaldehyde diethylacetal (14 g, 71 mmol) was heated to 100°C in the presence of *p*-toluenesulphonic acid (50 mg) until 7.9 mL of ethanol was distilled off. The reaction mixture was cooled and ether was added (150 mL) and washed with saturated

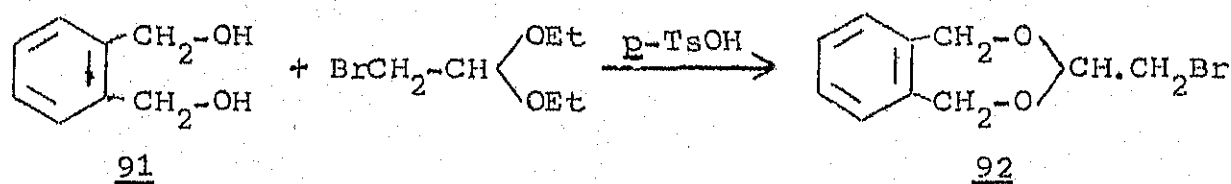
To a mixture of acetic anhydride (0.408 g, 4 mmol) and DMAP (0.244 g, 2 mmol) was added the ketene cyclic acetal 89 (0.568 g, 4 mmol). Heated the reaction mixture to 80-90°C with stirring for 2 h. Water (0.07 mL) was added and the heating was continued for two more hours. The crude product obtained after the usual work-up was purified by flash chromatography to yield 0.1 g of 50 (15%, elution with 5% ether-petroleum ether), 0.07 g of 90, m.p. 111-112°C (mixture m.p. with dehydroacetic acid, 111-112°C, elution with 1:19 ether-petroleum ether).

Dehydroacetic acid (90)

PMR (CDCl₃): 2.25 (s, 3H, -CH₃); 2.63 (s, 4H, CH₃, CH); 5.96 (s, 1H, vinylic).

MS (m/e): 168 (M⁺), 153, 125, 111, 98, 85, 69.

I.A.4.8a Preparation of 3-Bromomethyl-1,5-dihydro-2,4-benzodioxepin (92)



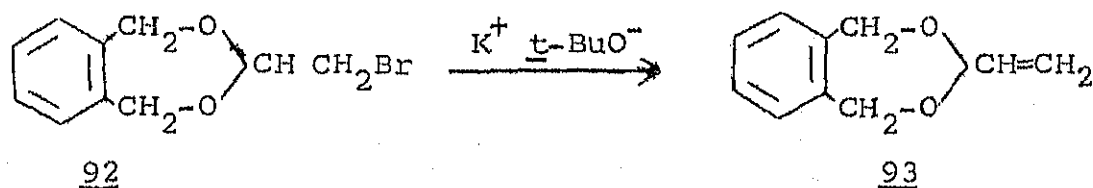
A mixture of phthalyl alcohol (91, 10 g, 72.5 mmol) and bromoacetaldehyde diethylacetal (14 g, 71 mmol) was heated to 100°C in the presence of p-toluenesulphonic acid (50 mg) until 7.9 mL of ethanol was distilled off. The reaction mixture was cooled and ether was added (150 mL) and washed with saturated

sodium bicarbonate solution (50 mL). The ether layer was dried over anhydrous sodium sulphate and filtered. The filtrate on concentration afforded 14 g (79%) of 92. Upon recrystallization from benzene, 92 melted at 98°C (lit.⁷⁸ m.p. 98°C).

PMR (CDCl₃): 3.42 (d, 2H, -CH₂); 4.86 (s, 4H, -CH₂); 5.05 (t, 1H, -CH); 7.2 (s, 4H, aromatic).

MS (m/e): 244, 242 (M⁺), 149, 121, 104, 91, 77.

I.A.4.8b Preparation of 3-Methylene-1,5-dihydro-2,4-benzodioxepin (93)



A solution of 92 (10 g, 41 mmol) in hot benzene was added rapidly with stirring at ca. 80°C to a solution of potassium tertiary butoxide (5.25 g, 43 mmol) in tert-butanol (70 mL). The resulting mixture was heated for 5 h at ca. 80°C. The excess tert-butanol was distilled under reduced pressure. Benzene was added to the residue and filtered. The filtrate was evaporated and the residue was recrystallized from benzene to yield 6.1 g (92%) of 93, m.p. 44°C (lit.⁷⁸ m.p. 44°C).

PMR (CDCl₃): 3.64 (s, 2H, vinylic); 5.0 (s, 4H, -CH₂); 7.06 (m, 4H, aromatic).

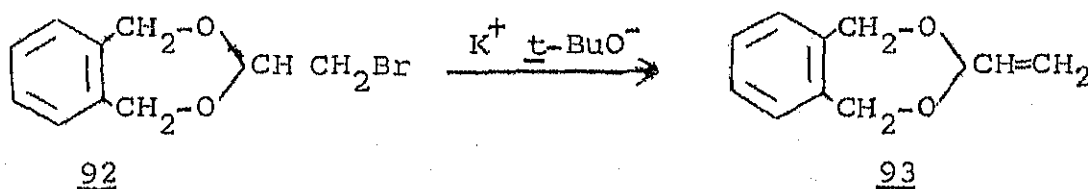
MS (m/e): 162 (M⁺), 149, 133, 119, 104, 91, 78, 65.

sodium bicarbonate solution (50 mL). The ether layer was dried over anhydrous sodium sulphate and filtered. The filtrate on concentration afforded 14 g (79%) of 92. Upon recrystallization from benzene, 92 melted at 98°C (lit.⁷⁸ m.p. 98°C).

PMR (CDCl₃): 3.42 (d, 2H, CH_2); 4.86 (s, 4H, CH_2); 5.05 (t, 1H, CH); 7.2 (s, 4H, aromatic).

MS (m/e): 244, 242 (M^+), 149, 121, 104, 91, 77.

I.A.4.8b Preparation of 3-Methylene-1,5-dihydro-2,4-benzodioxepin (93)

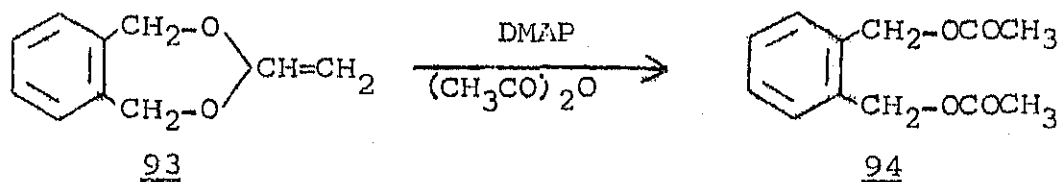


A solution of 92 (10 g, 41 mmol) in hot benzene was added rapidly with stirring at ca. 80°C to a solution of potassium tertiary butoxide (5.25 g, 43 mmol) in tert-butanol (70 mL). The resulting mixture was heated for 5 h at ca. 80°C. The excess tert-butanol was distilled under reduced pressure. Benzene was added to the residue and filtered. The filtrate was evaporated and the residue was recrystallized from benzene to yield 6.1 g (92%) of 93, m.p. 44°C (lit.⁷⁸ m.p. 44°C).

PMR (CDCl₃): 3.64 (s, 2H, vinylic); 5.0 (s, 4H, CH_2); 7.06 (m, 4H, aromatic).

MS (m/e): 162 (M^+), 149, 133, 119, 104, 91, 78, 65.

I.A.4.8c Reaction of 1,5-Dihydro-3-methylene-2,4-benzodioxepin (93) with Acetic anhydride and DMAP

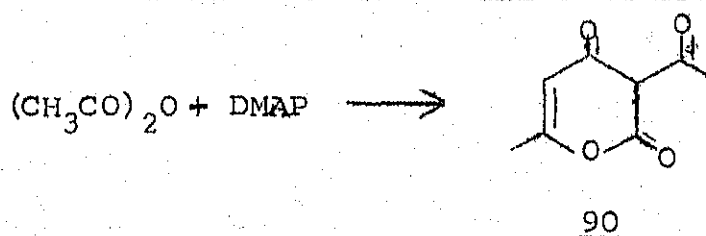


The compound 93 (0.648 g, 4 mmol) was treated under identical conditions with acetic anhydride (0.408 g, 4 mmol) and DMAP (0.244 g, 2 mmol) as done with 89. The crude product was subjected to flash chromatography to give 0.45 g of diacetate 94 (58%), m.p. 35°C (mixture m.p. 35°C, elution with petroleum ether).

IR (thin film): 1740 (ν $\text{C}=\text{O}$).

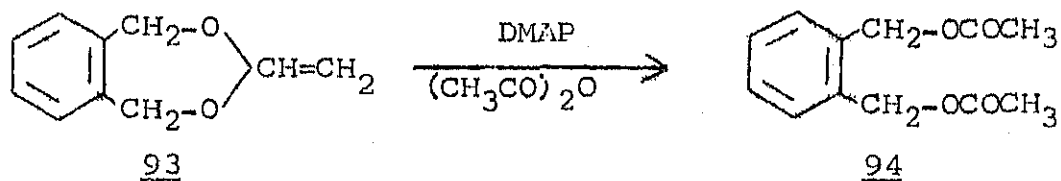
PMR (CDCl_3): 2.04 (s, 6H, $-\text{CH}_3$); 5.2 (s, 4H, $-\text{CH}_2$); 7.4 (s, 4H, aromatic).

I.A.4.9 Reaction of Acetic anhydride and 4-Dimethylaminopyridine



A mixture of acetic anhydride (0.22 g, 2.2 mmol) and DMAP (1.5 mmol, 0.183 g) was set aside at room temperature for two days. The crude product after the usual work-up was chromatographed over silica gel to yield 0.04 g of 90 (elution with

I.A.4.8c Reaction of 1,5-Dihydro-3-methylene-2,4-benzodioxepin (93) with Acetic anhydride and DMAP

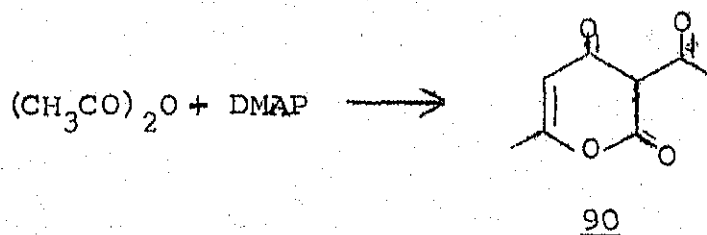


The compound 93 (0.648 g, 4 mmol) was treated under identical conditions with acetic anhydride (0.408 g, 4 mmol) and DMAP (0.244 g, 2 mmol) as done with 89. The crude product was subjected to flash chromatography to give 0.45 g of diacetate 94 (58%), m.p. 35°C (mixture m.p. 35°C, elution with petroleum ether).

IR (thin film): 1740 (ν $\text{C}=\text{O}$).

PMR (CDCl_3): 2.04 (s, 6H, $-\text{CH}_3$); 5.2 (s, 4H, $-\text{CH}_2$); 7.4 (s, 4H, aromatic).

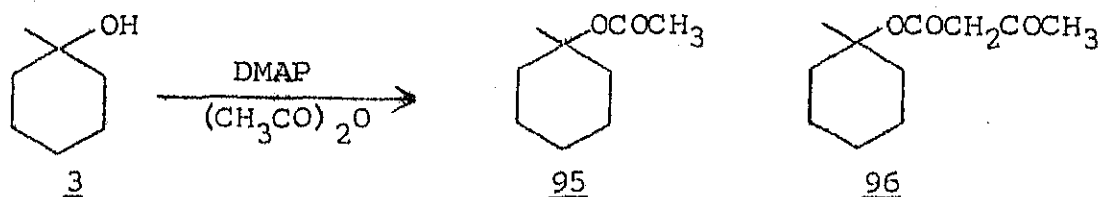
I.A.4.9 Reaction of Acetic anhydride and 4-Dimethylaminopyridine



A mixture of acetic anhydride (0.22 g, 2.2 mmol) and DMAP (1.5 mmol, 0.183 g) was set aside at room temperature for two days. The crude product after the usual work-up was chromatographed over silica gel to yield 0.04 g of 90 (elution with

1:19 ether petroleum ether), m.p. 111-112°C, (mixture m.p. 111-112°C).

I.A.4.10a Reaction of 1-Methylcyclohexanol (3) with Acetic anhydride and 4-Dimethylaminopyridine



To a mixture of acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol), added carbinol 3 (0.228 g, 2 mmol). The reaction mixture was heated with stirring at 85-90°C for 4 h. Methanol (0.5 mL) was added followed by water (10 mL). The stirring was continued for 0.25 h. The reaction mixture was extracted with dichloromethane (3 x 20 mL). The organic extract was washed with water (10 mL) followed by brine (10 mL) and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure to give a brown oil which was subjected to flash chromatography to yield 0.18 g of 95 (71%, elution with petroleum ether), 0.05 g of 96 (15%, elution with 1:19 ether-petroleum ether) and 0.04 g of recovered starting material.

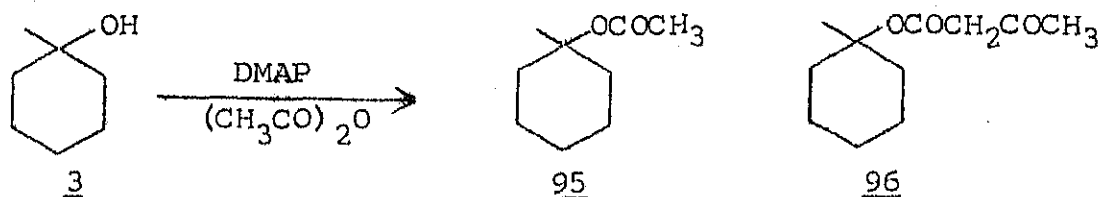
1-Methylcyclohexyl acetate (95)

IR (thin film): 1735 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.5 (m, 13H, $-\text{CH}_3$, $-\text{CH}_2$); 2.06 (s, 3H, $-\text{CH}_3$).

1:19 ether petroleum ether), m.p. 111-112°C, (mixture m.p. 111-112°C).

I.A.4.10a Reaction of 1-Methylcyclohexanol (3) with Acetic anhydride and 4-Dimethylaminopyridine



To a mixture of acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol), added carbinol 3 (0.228 g, 2 mmol). The reaction mixture was heated with stirring at 85-90°C for 4 h. Methanol (0.5 mL) was added followed by water (10 mL). The stirring was continued for 0.25 h. The reaction mixture was extracted with dichloromethane (3 x 20 mL). The organic extract was washed with water (10 mL) followed by brine (10 mL) and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure to give a brown oil which was subjected to flash chromatography to yield 0.18 g of 95 (71%, elution with petroleum ether), 0.05 g of 96 (15%, elution with 1:19 ether-petroleum ether) and 0.04 g of recovered starting material.

1-Methylcyclohexyl acetate (95)

IR (thin film): 1735 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.5 (m, 13H, $-\text{CH}_3$, $-\text{CH}_2$); 2.06 (s, 3H, $-\text{CH}_3$).

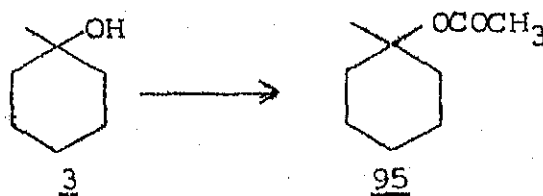
1-Methylcyclohexyl acetoacetate (96)

IR (CH_2Cl_2): 1710 ($\nu_{\text{C=O}}$) and 1735 ($\nu_{\text{C=O}}$).

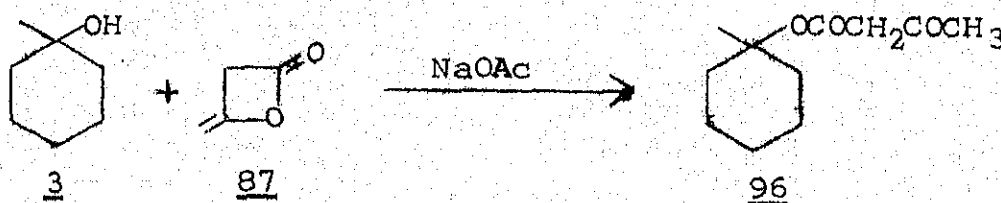
PMR (CDCl_3): 1.37 - 1.6 (s, br, 13H, $-\text{CH}_3$, $-\text{CH}_2$); 2.33 (s, 3H, $-\text{CH}_3$); 3.42 (s, 2H, $-\text{CH}_2$).

MS (m/e): 198 (M^+), 119, 114, 105, 99, 85, 81, 71, 58, 55, 43.

Exact Mass: Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3$: 198.1256. Found: 198.1256.

I.A.4.10b Preparation of 1-Methylcyclohexyl acetate (95)

To a solution of 3 (0.114 g, 1 mmol), DMAP (0.022 g, 0.1 mmol) and triethylamine (0.15 g, 1.5 mmol) in dichloromethane (5 mL) added acetic anhydride (0.2 g, 2 mmol) with stirring. The mixture was allowed to stand at room temperature for 15 h. The compound was partitioned between water and ether. The ether extract was washed with sodium bicarbonate solution followed by brine and dried over anhydrous sodium sulphate. Filtered the ether extract and concentrated to yield 0.137 g (88%) of 95.

I.A.4.10c Preparation of 1-Methylcyclohexyl acetoacetate (96)

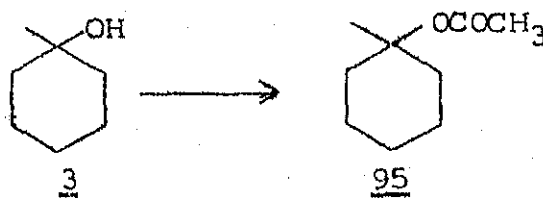
1-Methylcyclohexyl acetoacetate (96)

IR (CH_2Cl_2): 1710 ($\nu_{\text{C=O}}$) and 1735 ($\nu_{\text{C=O}}$).

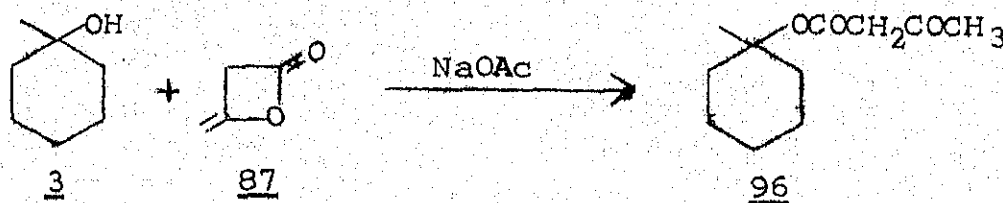
PMR (CDCl_3): 1.37 - 1.6 (s, br, 13H, $-\text{CH}_3$, $-\text{CH}_2$); 2.33 (s, 3H, $-\text{CH}_3$); 3.42 (s, 2H, $-\text{CH}_2$).

MS (m/e): 198 (M^+), 119, 114, 105, 99, 85, 81, 71, 58, 55, 43.

Exact Mass: Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3$: 198.1256. Found: 198.1256.

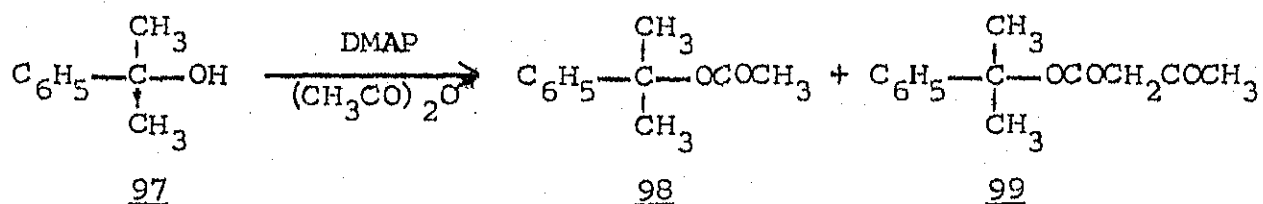
I.A.4.10b Preparation of 1-Methylcyclohexyl acetate (95)

To a solution of 3 (0.114 g, 1 mmol), DMAP (0.022 g, 0.1 mmol) and triethylamine (0.15 g, 1.5 mmol) in dichloromethane (5 mL) added acetic anhydride (0.2 g, 2 mmol) with stirring. The mixture was allowed to stand at room temperature for 15 h. The compound was partitioned between water and ether. The ether extract was washed with sodium bicarbonate solution followed by brine and dried over anhydrous sodium sulphate. Filtered the ether extract and concentrated to yield 0.137 g (88%) of 95.

I.A.4.10c Preparation of 1-Methylcyclohexyl acetoacetate (96)

A solution of alcohol 3 (0.371 g, 3.25 mmol) and diketene (0.336 g, 4 mmol) in benzene was refluxed for 12 h with a catalytic amount of anhydrous sodium acetate. The reaction mixture was cooled and then poured into water (10 mL). The mixture was extracted with ether (2 x 15 mL). The ether extract was dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give the acetoacetate 96 as a colourless oil (0.51 g, 80%).

I.A.4.11a Reaction of tert-Alcohol 97 with Acetic anhydride and 4-Dimethylaminopyridine



Reaction was carried out under identical conditions as above with dimethylphenyl carbinol (97, 0.272 g, 2 mmol), acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol). The crude product obtained from the usual work-up was purified by flash chromatography to yield 0.17 g of 98 (66.0%, elution with petroleum ether), 0.08 g of 99 (18.0%, elution with 1:19 ether-petroleum ether).

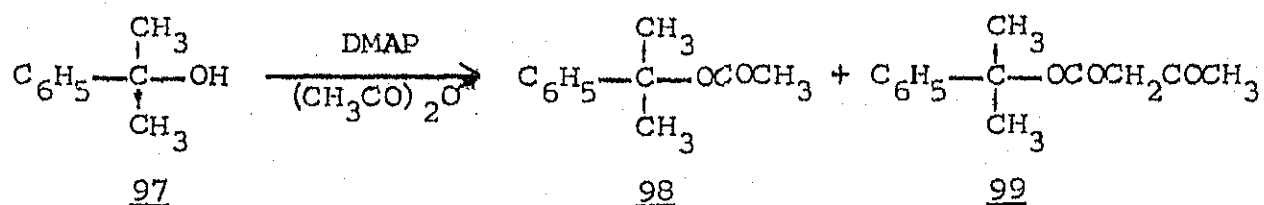
2-Acetoxy-2-phenylpropane (98)

IR (thin film): 1735 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.65 (s, 6H, $-\text{CH}_3$); 1.88 (s, 3H, $-\text{CH}_3$); 7.25

A solution of alcohol 3 (0.371 g, 3.25 mmol) and diketene (0.336 g, 4 mmol) in benzene was refluxed for 12 h with a catalytic amount of anhydrous sodium acetate. The reaction mixture was cooled and then poured into water (10 mL). The mixture was extracted with ether (2 x 15 mL). The ether extract was dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give the acetoacetate 96 as a colourless oil (0.51 g, 80%).

I.A.4.11a Reaction of tert-Alcohol 97 with Acetic anhydride and 4-Dimethylaminopyridine



Reaction was carried out under identical conditions as above with dimethylphenyl carbinol (97, 0.272 g, 2 mmol), acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol). The crude product obtained from the usual work-up was purified by flash chromatography to yield 0.17 g of 98 (66.0%, elution with petroleum ether), 0.08 g of 99 (18.0%, elution with 1:19 ether-petroleum ether).

2-Acetoxy-2-phenylpropane (98)

IR (thin film): 1735 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.65 (s, 6H, $-\text{CH}_3$); 1.88 (s, 3H, $-\text{CH}_3$); 7.25 (m, 5H, aromatic).

MS (m/e): 118 ($M^+ - \text{CH}_3\text{COOH}$), 117, 103, 91, 78, 60, 45, 43.

2-Acetoacetoxy-2-phenylpropane (99)

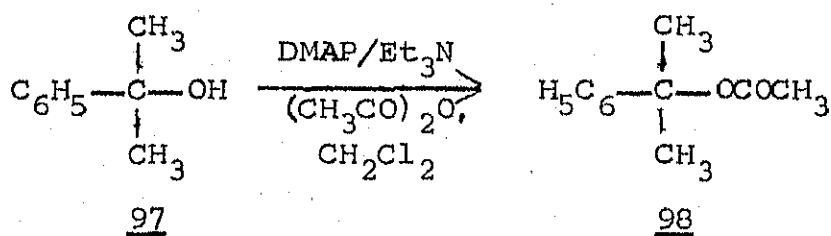
IR (thin film): 1715 ($\nu_{\text{C=O}}$) and 1740 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.84 (s, 6H, $-\text{CH}_3$); 2.26 (s, 3H, $-\text{CH}_3$); 3.45 (s, 2H, $-\text{CH}_2-$); 7.43 (m, 5H, aromatic).

MS (m/e): 220 (M^+), 136, 119, 117, 91, 85, 77, 43.

Exact Mass: Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$: 220.1100. Found: 220.1104.

I.A.4.11b Preparation of Acetate 98



Acetic anhydride (0.765 g, 7.5 mmol) was added with stirring to a solution containing alcohol 97 (0.62 g, 5 mmol), triethylamine (0.757 g, 7.5 mmol) and DMAP (0.048 g, 0.4 mmol) in dry dichloromethane (20 mL). The mixture was stirred at ambient temperature for 20 h. Methanol (1 mL) was added, followed by water (25 mL). After stirring for 0.25 h, the mixture was extracted with ether (3 x 30 mL). The ether extract was washed with water (20 mL) followed by brine (20 mL) and dried over anhydrous magnesium sulphate. The solvent was evaporated to yield 0.7 g of 98 (86.0%).

MS (m/e): 118 ($M^+ - \text{CH}_3\text{COOH}$), 117, 103, 91, 78, 60, 45, 43.

2-Acetoacetoxy-2-phenylpropane (99)

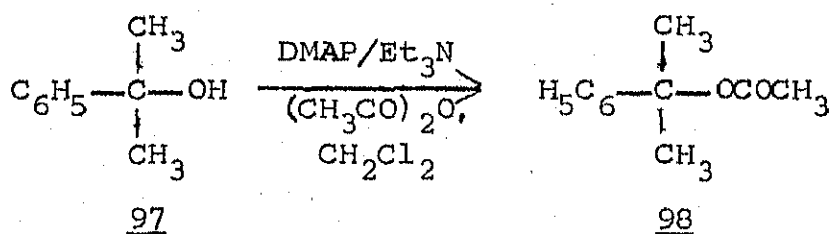
IR (thin film): 1715 ($\nu_{\text{C=O}}$) and 1740 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.84 (s, 6H, $-\text{CH}_3$); 2.26 (s, 3H, $-\text{CH}_3$); 3.45 (s, 2H, $-\text{CH}_2-$); 7.43 (m, 5H, aromatic).

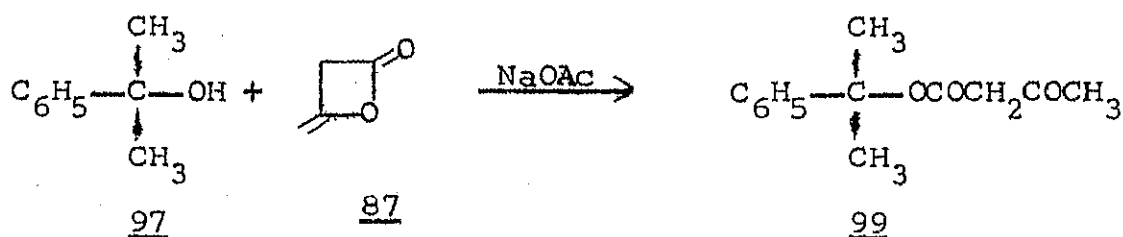
MS (m/e): 220 (M^+), 136, 119, 117, 91, 85, 77, 43.

Exact Mass: Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$: 220.1100. Found: 220.1104.

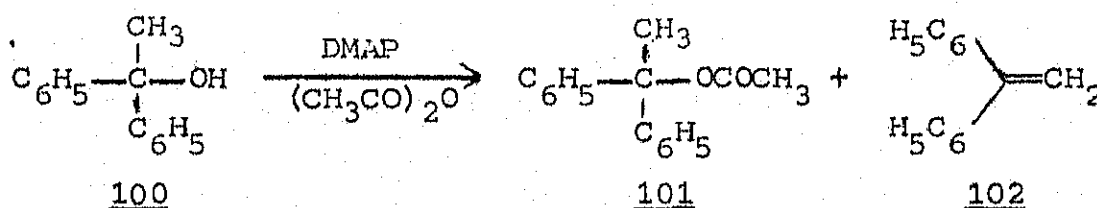
I.A.4.11b Preparation of Acetate 98



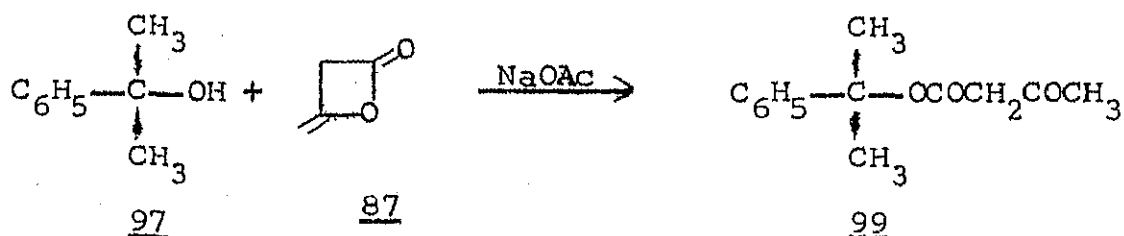
Acetic anhydride (0.765 g, 7.5 mmol) was added with stirring to a solution containing alcohol 97 (0.62 g, 5 mmol), triethylamine (0.757 g, 7.5 mmol) and DMAP (0.048 g, 0.4 mmol) in dry dichloromethane (20 mL). The mixture was stirred at ambient temperature for 20 h. Methanol (1 mL) was added, followed by water (25 mL). After stirring for 0.25 h, the mixture was extracted with ether (3 x 30 mL). The ether extract was washed with water (20 mL) followed by brine (20 mL) and dried over anhydrous magnesium sulphate. The solvent was evaporated to yield 0.7 g of 98 (86.0%).

I.A.4.11c Preparation of Acetoacetate 99

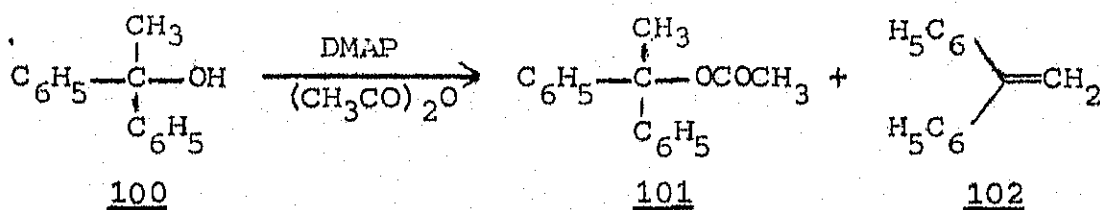
A benzene solution containing alcohol 97 (0.352 g, 2.83 mmol), diketene (0.26 g, 3.1 mmol) and sodium acetate (0.04 g, 0.5 mmol) was refluxed for 3 h. The reaction mixture was cooled and poured into water (20 mL). The mixture was extracted with ether and the extract was dried over anhydrous magnesium sulphate. The solvent was evaporated to yield 0.525 g of the acetoacetate 99 (84.3%) as a colourless oil.

I.A.4.12 Reaction of the *tert*-Alcohol 100 with Acetic anhydride and 4-Dimethylaminopyridine

The tertiary alcohol 100 (0.396 g, 2 mmol) was treated under identical conditions as in the earlier examples with acetic anhydride (0.44 g, 4.4 mmol) and dimethylaminopyridine (0.244 g, 2 mmol). The brown liquid obtained after the work-up was purified using flash chromatography technique to yield 0.13 g of 102 (52%, elution with petroleum ether), 0.345 g of 101 (46%, elution with

I.A.4.11c Preparation of Acetoacetate 99

A benzene solution containing alcohol 97 (0.352 g, 2.83 mmol), diketene (0.26 g, 3.1 mmol) and sodium acetate (0.04 g, 0.5 mmol) was refluxed for 3 h. The reaction mixture was cooled and poured into water (20 mL). The mixture was extracted with ether and the extract was dried over anhydrous magnesium sulphate. The solvent was evaporated to yield 0.525 g of the acetoacetate 99 (84.3%) as a colourless oil.

I.A.4.12 Reaction of the *tert*-Alcohol 100 with Acetic anhydride and 4-Dimethylaminopyridine

The tertiary alcohol 100 (0.396 g, 2 mmol) was treated under identical conditions as in the earlier examples with acetic anhydride (0.44 g, 4.4 mmol) and dimethylaminopyridine (0.244 g, 2 mmol). The brown liquid obtained after the work-up was purified using flash chromatography technique to yield 0.13 g of 102 (52%, elution with petroleum ether), 0.345 g of 101 (46%, elution with

petroleum ether) and 0.11 g of unreacted starting alcohol (elution with 1:19 ether-petroleum ether).

1,1-Diphenylethylene 102

IR (thin film): 1660 and 1600 ($\nu_{C=C}$).

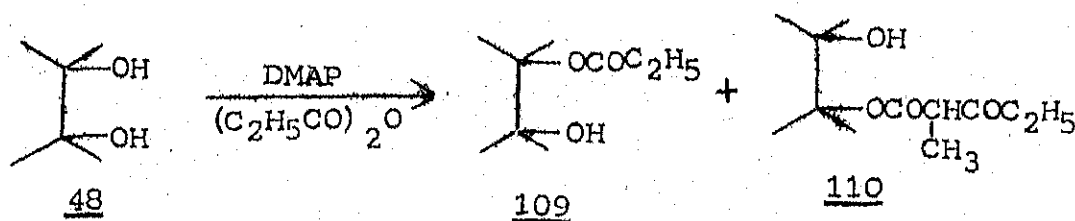
PMR ($CDCl_3$): 5.39 (s, 2H, vinylic); 7.23 (s, 10 H, aromatic).

1,1-Diphenylethyl acetate 101

IR (thin film): 1740 ($\nu_{C=O}$).

PMR ($CDCl_3$): 2.09 (s, 3H, $-CH_3$); 2.19 (s, 3H, $-CH_3$); 7.3 (s, 10 H, aromatic).

I.A.4.13 Reaction of Pinacol 48 with Propionic anhydride and 4-Dimethylaminopyridine



To a mixture of propionic anhydride (0.858 g, 6.6 mmol) and DMAP (0.366 g, 3 mmol), was added pinacol 48 (0.354 g, 3 mmol). The reaction mixture was heated with stirring for 4 h. The usual work-up as in the earlier cases afforded a brown oil which was purified by flash chromatography to give 0.30 g of 109 (72.0%, elution with 1:19 ether-petroleum ether),

petroleum ether) and 0.11 g of unreacted starting alcohol (elution with 1:19 ether-petroleum ether).

1,1-Diphenylethylene 102

IR (thin film): 1660 and 1600 ($\nu_{C=C}$).

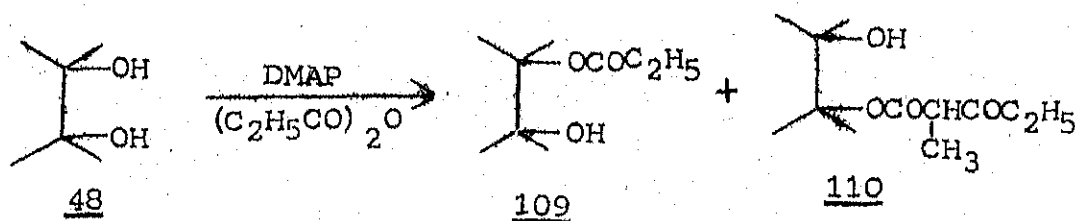
PMR ($CDCl_3$): 5.39 (s, 2H, vinylic); 7.23 (s, 10 H, aromatic).

1,1-Diphenylethyl acetate 101

IR (thin film): 1740 ($\nu_{C=O}$).

PMR ($CDCl_3$): 2.09 (s, 3H, $-CH_3$); 2.19 (s, 3H, $-CH_3$); 7.3 (s, 10 H, aromatic).

I.A.4.13 Reaction of Pinacol 48 with Propionic anhydride and 4-Dimethylaminopyridine



To a mixture of propionic anhydride (0.858 g, 6.6 mmol) and DMAP (0.366 g, 3 mmol), was added pinacol 48 (0.354 g, 3 mmol). The reaction mixture was heated with stirring for 4 h. The usual work-up as in the earlier cases afforded a brown oil which was purified by flash chromatography to give 0.30 g of 109 (72.0%, elution with 1:19 ether-petroleum ether),

0.085 g of 110 (15%, elution with 1:19 ether-petroleum ether) and 0.07 g of unreacted pinacol (elution with 1:5 ether-petroleum ether).

Compound 109

IR (thin film): 1730 ($\nu_{\text{C=O}}$).

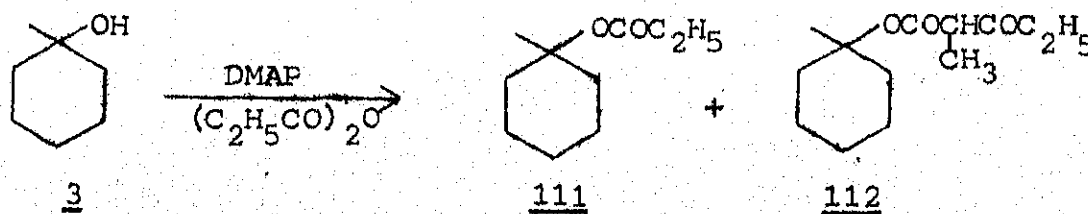
PMR (CDCl_3): 1.06 (t, 3H, $-\text{CH}_3$, $J = 7.5$ Hz); 1.1 (s, 6H, $-\text{CH}_3$); 1.4 (s, 6H, $-\text{CH}_3$); 2.23 (q, 2H, $-\text{CH}_2$, $J = 7.5$ Hz); 2.9 (s, 1H, $-\text{OH}$, D_2O exchangeable).

Compound 110

IR (CHCl_3): 1735 ($\nu_{\text{C=O}}$) and 1710 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.03 (t, 3H, $-\text{CH}_3$, $J = 7.5$ Hz); 1.1 (s, 6H, $-\text{CH}_3$); 1.27 (d, 3H, $-\text{CH}_3$, $J = 6$ Hz); 1.45 (s, 6H, $-\text{CH}_3$); 2.47 (q, 2H, $-\text{CH}_2$, $J = 7.5$ Hz); 3.35 (q, 1H, $-\text{CH}$, $J = 6$ Hz).

I.A.4.14 Reaction of 1-Methylcyclohexanol (3) with Propionic anhydride and 4-Dimethylaminopyridine



The tertiary alcohol 3 (0.228 g, 2 mmol) was added with stirring to a mixture of propionic anhydride (0.572 g, 4.4 mmol)

0.085 g of 110 (15%, elution with 1:19 ether-petroleum ether) and 0.07 g of unreacted pinacol (elution with 1:5 ether-petroleum ether).

Compound 109

IR (thin film): 1730 ($\nu_{\text{C=O}}$).

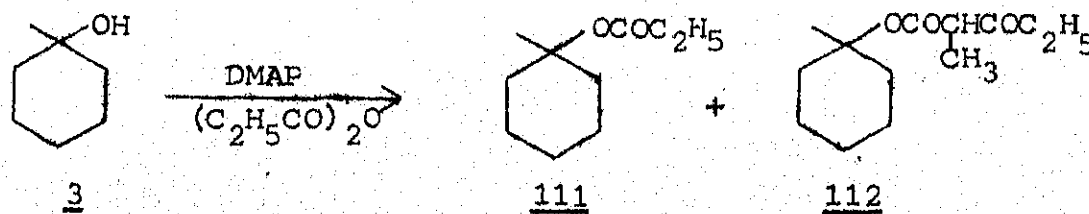
PMR (CDCl_3): 1.06 (t, 3H, $-\text{CH}_3$, $J = 7.5$ Hz); 1.1 (s, 6H, $-\text{CH}_3$); 1.4 (s, 6H, $-\text{CH}_3$); 2.23 (q, 2H, $-\text{CH}_2$, $J = 7.5$ Hz); 2.9 (s, 1H, $-\text{OH}$, D_2O exchangeable).

Compound 110

IR (CHCl_3): 1735 ($\nu_{\text{C=O}}$) and 1710 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 1.03 (t, 3H, $-\text{CH}_3$, $J = 7.5$ Hz); 1.1 (s, 6H, $-\text{CH}_3$); 1.27 (d, 3H, $-\text{CH}_3$, $J = 6$ Hz); 1.45 (s, 6H, $-\text{CH}_3$); 2.47 (q, 2H, $-\text{CH}_2$, $J = 7.5$ Hz); 3.35 (q, 1H, $-\text{CH}$, $J = 6$ Hz).

I.A.4.14 Reaction of 1-Methylcyclohexanol (3) with Propionic anhydride and 4-Dimethylaminopyridine



The tertiary alcohol 3 (0.228 g, 2 mmol) was added with stirring to a mixture of propionic anhydride (0.572 g, 4.4 mmol)

and DMAP (0.244 g, 2 mmol). The reaction mixture was heated to 85–90°C for 4 h. The reaction mixture was worked up as earlier to afford a brown oil which was subjected to flash chromatography to yield 0.2 g of 111 (75.0%, elution with petroleum ether), 0.07 g of 112 (21.0%, elution with petroleum ether) and 0.05 g of the unreacted alcohol (elution with 1:19 ether-petroleum ether).

Propionate 111

IR (thin film): 1730 ($\nu_{\text{C=O}}$).

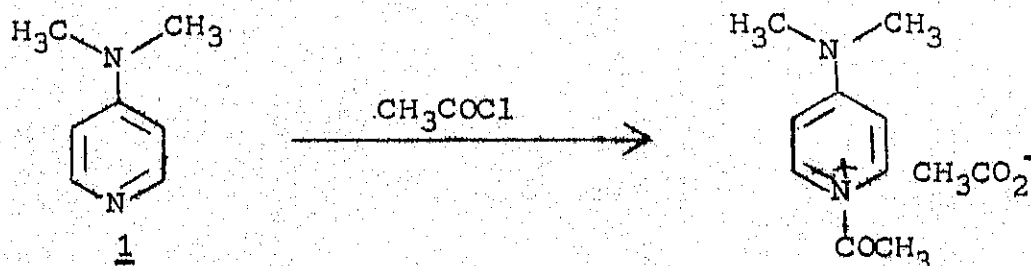
PMR (CCl_4): 1.1 (t, 3H, $-\text{CH}_3$, $J = 7$ Hz); 1.43 (s, br, 13H, $-\text{CH}_3$, $-\text{CH}_2$); 2.23 (q, 2H, $-\text{CH}_2$, $J = 7$ Hz).

Compound 112

IR (CCl_4): 1710 ($\nu_{\text{C=O}}$) and 1730 ($\nu_{\text{C=O}}$).

PMR (CCl_4): 1.1 (t, 3H, $-\text{CH}_3$, $J = 6$ Hz); 1.3 (d, 3H, $-\text{CH}_3$, $J = 6$ Hz); 1.5 (s, br, 13H, $-\text{CH}_3$, $-\text{CH}_2$); 2.5 (q, 2H, $-\text{CH}_2$, $J = 6$ Hz); 3.37 (q, 1H, $-\text{CH}$, $J = 6$ Hz).

I.A.4.15a Reaction of Dimethylaminopyridine and Acetyl Chloride in Petroleum Ether



and DMAP (0.244 g, 2 mmol). The reaction mixture was heated to 85–90°C for 4 h. The reaction mixture was worked up as earlier to afford a brown oil which was subjected to flash chromatography to yield 0.2 g of 111 (75.0%, elution with petroleum ether), 0.07 g of 112 (21.0%, elution with petroleum ether) and 0.05 g of the unreacted alcohol (elution with 1:19 ether-petroleum ether).

Propionate 111

IR (thin film): 1730 ($\nu_{\text{C=O}}$).

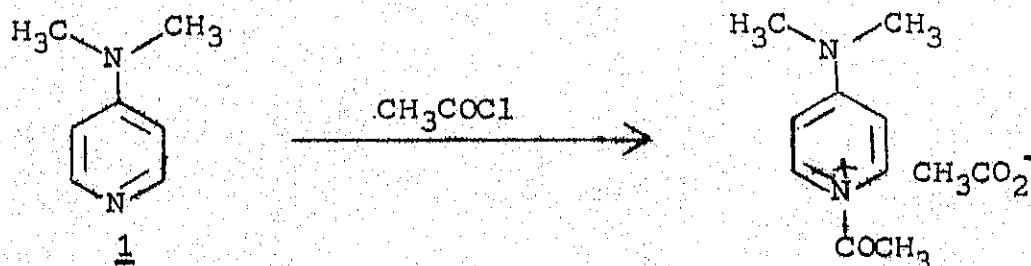
PMR (CCl_4): 1.1 (t, 3H, $-\text{CH}_3$, $J = 7$ Hz); 1.43 (s, br, 13H, $-\text{CH}_3$, $-\text{CH}_2$); 2.23 (q, 2H, $-\text{CH}_2$, $J = 7$ Hz).

Compound 112

IR (CCl_4): 1710 ($\nu_{\text{C=O}}$) and 1730 ($\nu_{\text{C=O}}$).

PMR (CCl_4): 1.1 (t, 3H, $-\text{CH}_3$, $J = 6$ Hz); 1.3 (d, 3H, $-\text{CH}_3$, $J = 6$ Hz); 1.5 (s, br, 13H, $-\text{CH}_3$, $-\text{CH}_2$); 2.5 (q, 2H, $-\text{CH}_2$, $J = 6$ Hz); 3.37 (q, 1H, $-\text{CH}$, $J = 6$ Hz).

I.A.4.15a Reaction of Dimethylaminopyridine and Acetyl Chloride in Petroleum Ether



To a suspension of DMAP (0.244 g, 2 mmol) in dry petroleum ether added slowly acetyl chloride (0.157 g, 0.14 ml, 2 mmol) with stirring. A white precipitate immediately coagulated in the solution which was stirred for 2 h at room temperature. The hygroscopic solid 41a was filtered and washed thoroughly with dry petroleum ether (0.357 g, 89%).

IR (KBr) : 1650 (ν $\text{C}=\text{N}$).

PMR (CDCl_3) : 2.1 (s, $-\text{CH}_2-$), 2.23 (s, $-\text{CH}_3$), 3.15 (s, 6H, N- CH_3); 6.6 (d, 2H, aromatic), 8.16 (d, 2H, aromatic); 14.5 (s, -NH).
(within 0.25 h after dissolution)

I.A.4.15b Reaction of 41a with Aniline

To a solution of aniline (0.093 g, 1 mmol) in dichloromethane (10 mL) was added 1-acetyl-4-dimethylaminopyridinium chloride (41a, 0.401 g, 2 mmol) and stirred for 8 h at room temperature. Water was added (5 mL) and the reaction mixture was extracted with ether. The ether extract was dried and evaporated to afford 0.085 g of acetanilide (63%), m.p. 114°C (mixture m.p. 114°C).

To a suspension of DMAP (0.244 g, 2 mmol) in dry petroleum ether added slowly acetyl chloride (0.157 g, 0.14 ml, 2 mmol) with stirring. A white precipitate immediately coagulated in the solution which was stirred for 2 h at room temperature. The hygroscopic solid 41a was filtered and washed thoroughly with dry petroleum ether (0.357 g, 89%).

IR (KBr) : 1650 (ν $\text{C}=\text{N}$).

PMR (CDCl_3) : 2.1 (s, $-\text{CH}_2$), 2.23 (s, $-\text{CH}_3$), 3.15 (s, 6H, N- CH_3); 6.6 (d, 2H, aromatic), 8.16 (d, 2H, aromatic); 14.5 (s, -NH).
(within 0.25 h after dissolution)

I.A.4.15b Reaction of 41a with Aniline

To a solution of aniline (0.093 g, 1 mmol) in dichloromethane (10 mL) was added 1-acetyl-4-dimethylaminopyridinium chloride (41a, 0.401 g, 2 mmol) and stirred for 8 h at room temperature. Water was added (5 mL) and the reaction mixture was extracted with ether. The ether extract was dried and evaporated to afford 0.085 g of acetanilide (63%), m.p. 114°C (mixture m.p. 114°C).

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CHAPTER I

(PART B)

STUDIES IN MOLECULAR REARRANGEMENT: A SHORT SYNTHESIS OF KARAHANAENONE

I.B.1 ABSTRACT

The reductive coupling reaction of carbonyl compounds mediated by low-valent titanium species has been efficiently used in the synthesis of the unsymmetrical pinacol, 1-(2'-hydroxypropyl)-4-methyl-3-cyclohexenol. This key intermediate underwent a smooth ring expansion with boron trifluoride etherate resulting in a short synthesis of Karahanaenone, an odoriferous constituent of Japanese hop and Cypress oil. A new methodology has been developed for the synthesis of the versatile synthon, 4-methyl-3-cyclohexenone.

I.B.2 INTRODUCTION

The reductive coupling of carbonyl compounds constitute an important method for the formation of carbon-carbon bonds.¹

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I.B.2 INTRODUCTION

The reductive coupling of carbonyl compounds constitute an important method for the formation of carbon-carbon bonds.¹

The coupling of carboxylic esters (acyloin reaction) has long been recognized as a powerful tool for intermolecular condensations. The classical methods involve the use of Al-Hg and Mg-Hg to effect such coupling reactions.^{2,3} Several procedures have been reported in the literature to couple aromatic carbonyl compounds using low-valent transition metal reagents.⁴⁻⁷ However, the reagent system developed by McMurry and coworkers, ($\text{TiCl}_3/\text{LiAlH}_4$), was found to give excellent yields in the case of both aryl and alkyl substituted carbonyl compounds. All these methodologies lead to the corresponding olefins rather than the pinacols.⁸⁻¹⁰ Aromatic carbonyl compounds were found to yield pinacols by the reaction with chlorotrimethylsilane and magnesium in HMPA.¹¹ Corey et al. have found that ketones and aldehydes were consistently coupled in excellent yields by the Ti(II) species generated by the reaction of titanium tetrachloride and amalgamated magnesium (70-80 mesh), to yield pinacols.¹² Recently, it has been shown that aromatic aldehydes and ketones undergo rapid one-electron reduction to pinacols with aqueous titanium trichloride in basic media.¹³ Reductive coupling of carbonyl compounds to pinacols has also been achieved using low-valent cerium.¹⁴ An important feature of the low-valent cerium reagent is that it can be applied successfully even in the presence of other reducible functional groups like ester and nitrile.

The Ti(II) species derived from titanium tetrachloride and amalgamated magnesium has been shown to be a versatile

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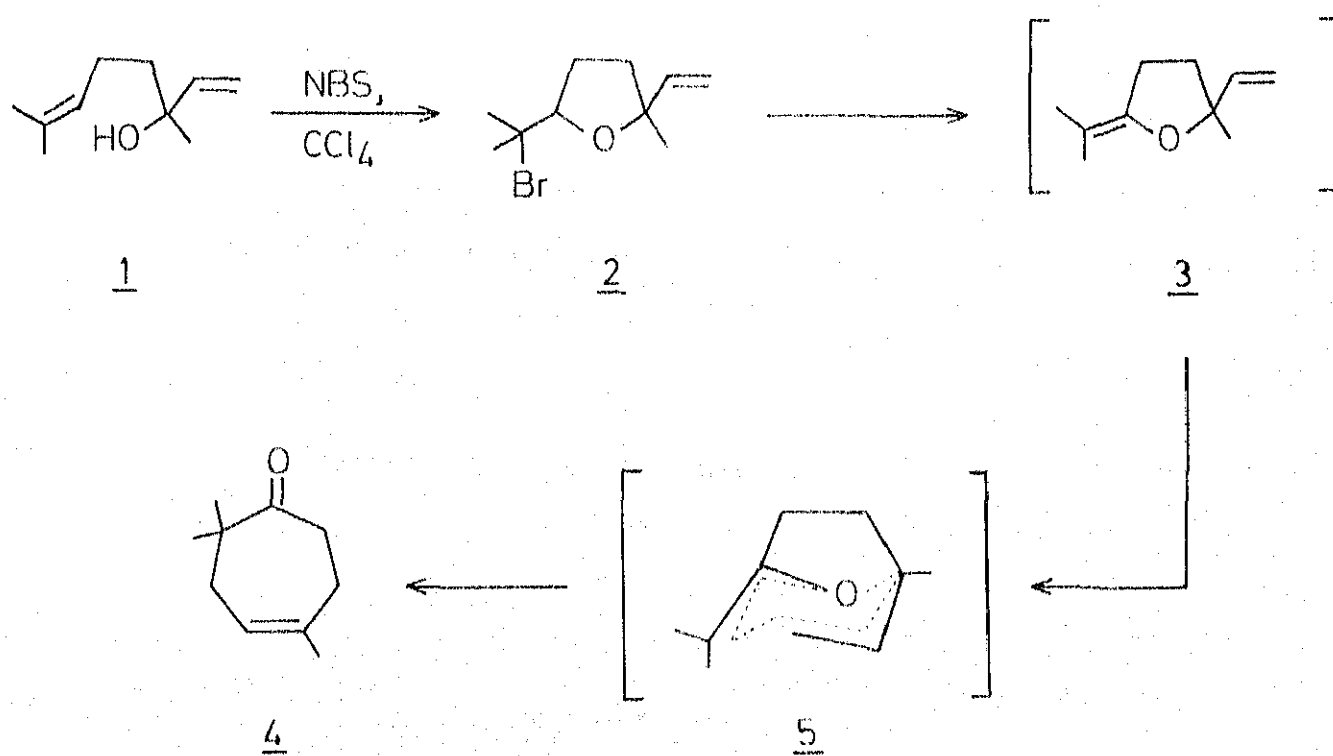
reagent in the intermolecular and intramolecular pinacolic coupling of carbonyl compounds.¹² It was felt that the potential usefulness of this reagent has not been completely explored. Our interest in the chemistry of low-valent transition metal reagents prompted us to look into the scope and utility of such pinacolic coupling reaction of carbonyl compounds in a study directed towards a short synthesis of Karahanaenone (4).

Karahanaenone (4) is an odoriferous constituent of Japanese hop and Cypress oil, Cupressus sempervirens.¹⁵ Ever since the isolation and characterization of this seven-membered monoterpene 4, several syntheses of this natural product have been reported.¹⁶⁻²² Demole and Enggist described the first synthesis of 4.¹⁶ They found that linalool (1), on treatment with N-bromosuccinamide in carbon tetrachloride gave the bromo ether 2. This underwent a smooth dehydrobromination in refluxing collidine to give rise to an intermediate, allylvinyl ether 3, which rearranged directly to Karahanaenone (4), through a [3,3] sigmatropic process (Scheme I.B.1). Wender, while developing a general methodology for the direct formation of functionalized seven-membered carbocycles, applied his strategy to the synthesis of Karahanaenone (4) (Scheme I.B.2).¹⁷ A group of Japanese workers intrigued by the possibility of effecting cationic cyclization via nucleophilic participation of silyl enol ethers, applied their strategy in the synthesis of the

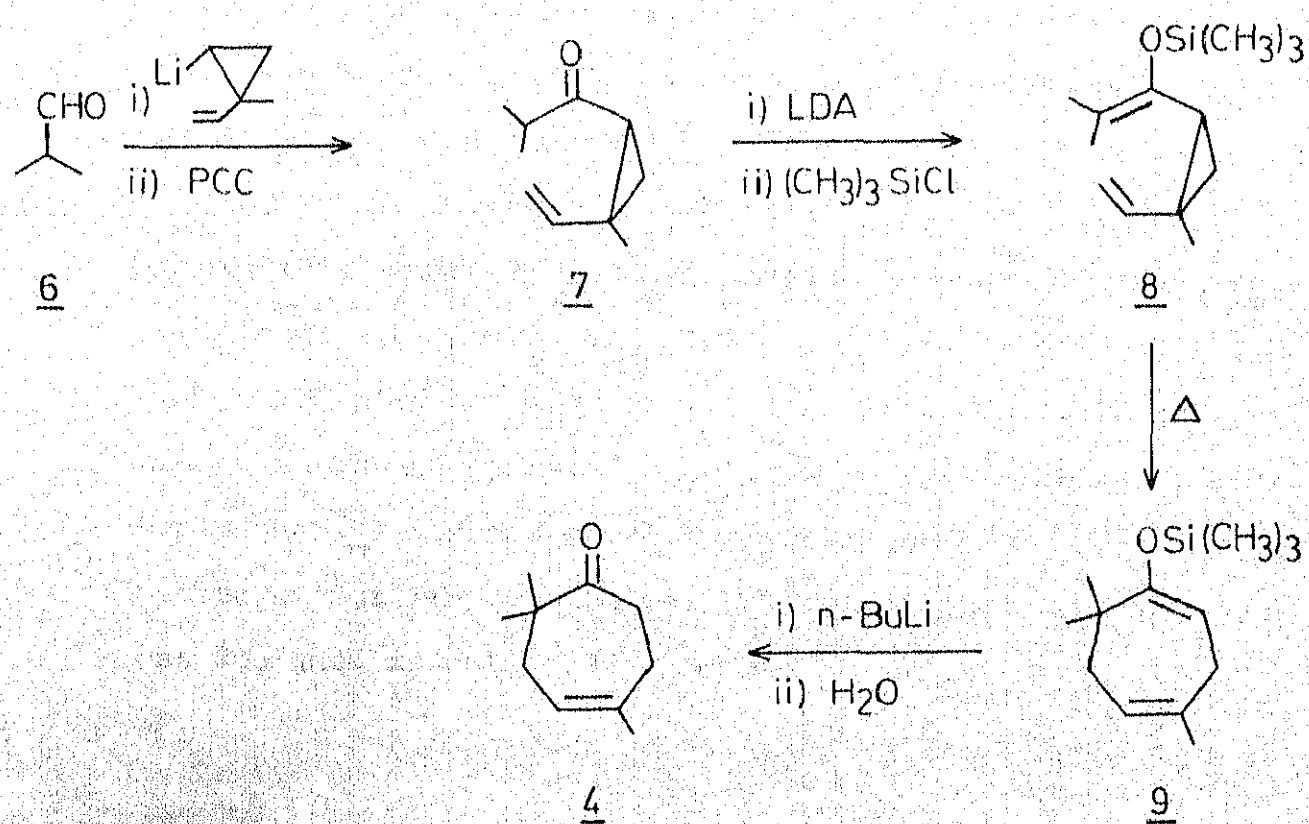
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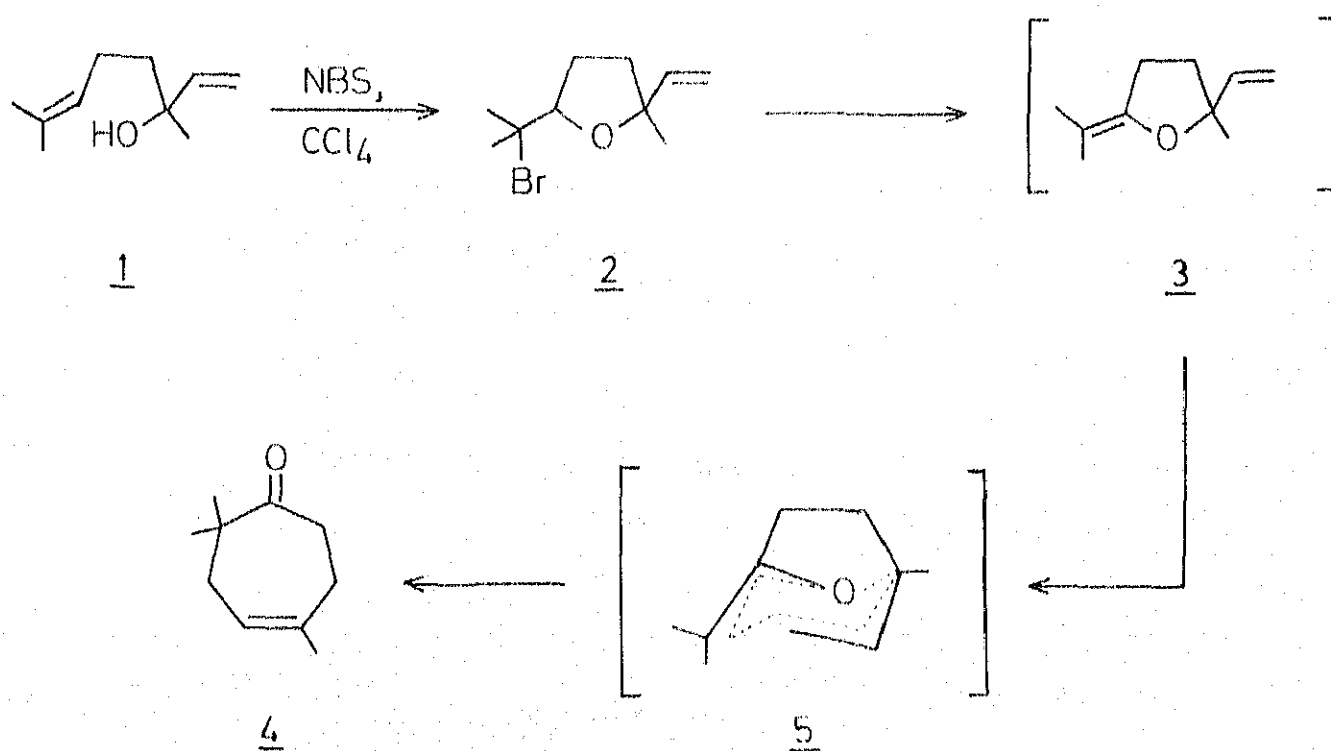
Scheme I.B.1



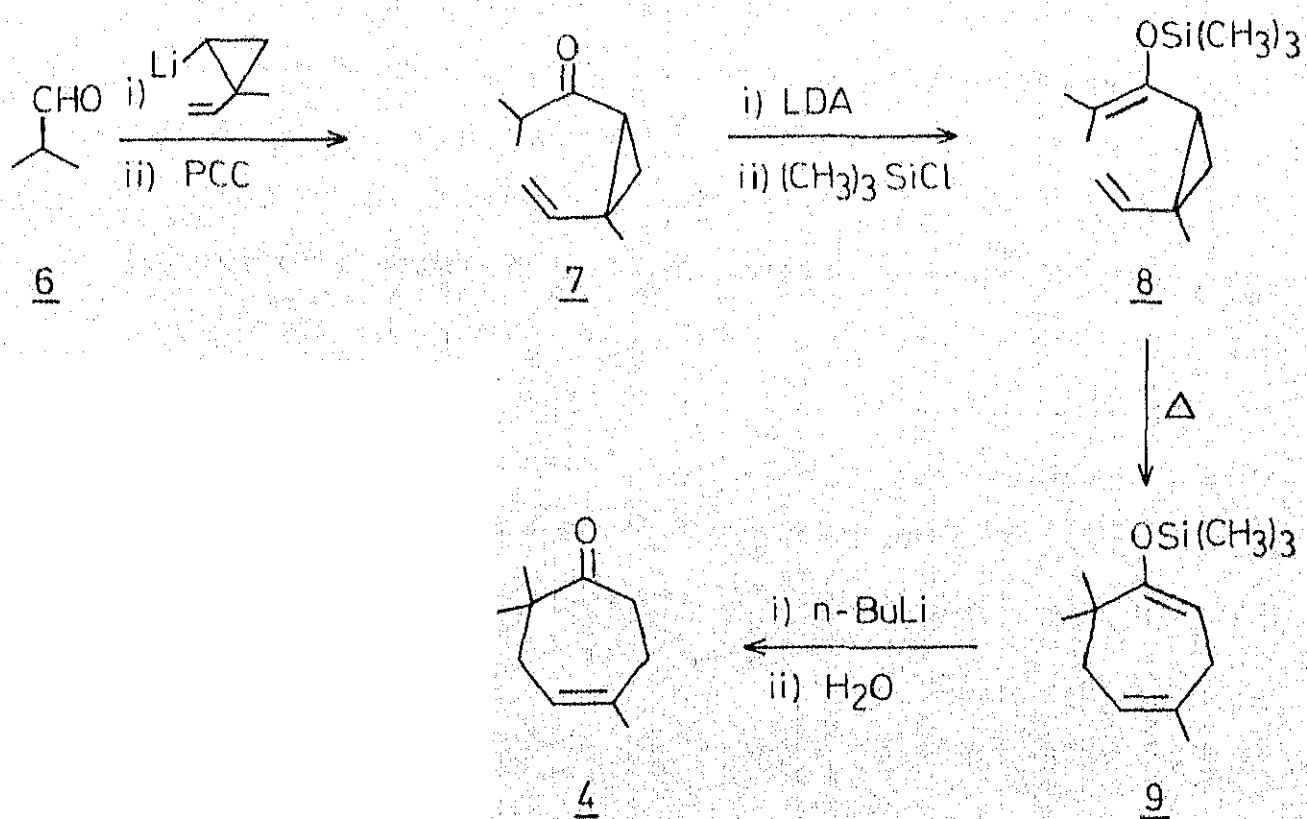
Scheme I.B.2



Scheme I.B.1



Scheme I.B.2



7-ring monoterpene 4 (Scheme I.B.3).¹⁸ Karahanaenone (4) was also synthesized to demonstrate the silver ion induced $3+4 \rightarrow 7$ carbocyclic reaction.²⁰ Thus, 1,1-dimethyl-2-trimethylsiloxyallyl chloride in the presence of isoprene gave a mixture of Karahanaenone (4) and its isomer 17, in the ratio of 2.5:1 (Scheme I.B.4).

Karahanaenone (4) has usually been used as a target molecule to exemplify a new methodology, as is reflected from the reported syntheses.

I.B.3 RESULTS AND DISCUSSION

The objective of the present study has been to explore the potential usefulness of the titanium(II) mediated intermolecular pinacolic coupling reaction to form a key intermediate, which can subsequently be rearranged to Karahanaenone (4). The reductive coupling method has been shown to be effective in the synthesis of unsymmetrical pinacols.¹² It was decided therefore, to use this methodology to synthesize the unsymmetrical pinacol, 1-(2'-hydroxypropyl)-4-methyl-3-cyclohexenol (20). This compound was anticipated to serve as the key intermediate in the synthesis of the seven-membered monoterpene, 2,2,5-trimethyl-4-cycloheptenone (4), if the pinacol rearrangement could be carried out to effect ring expansion. The synthetic strategy which was designed is outlined in Scheme I.B.5.

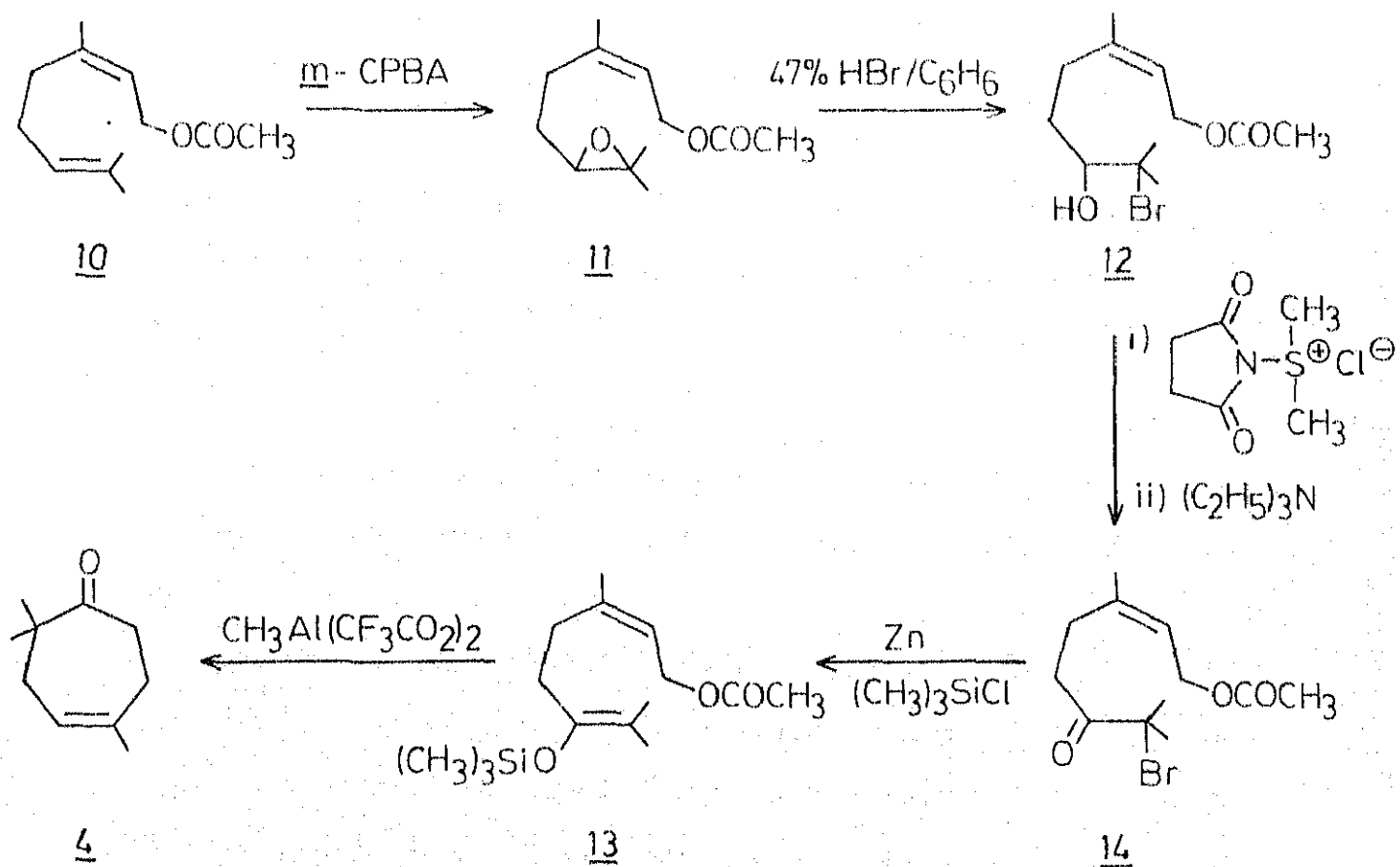
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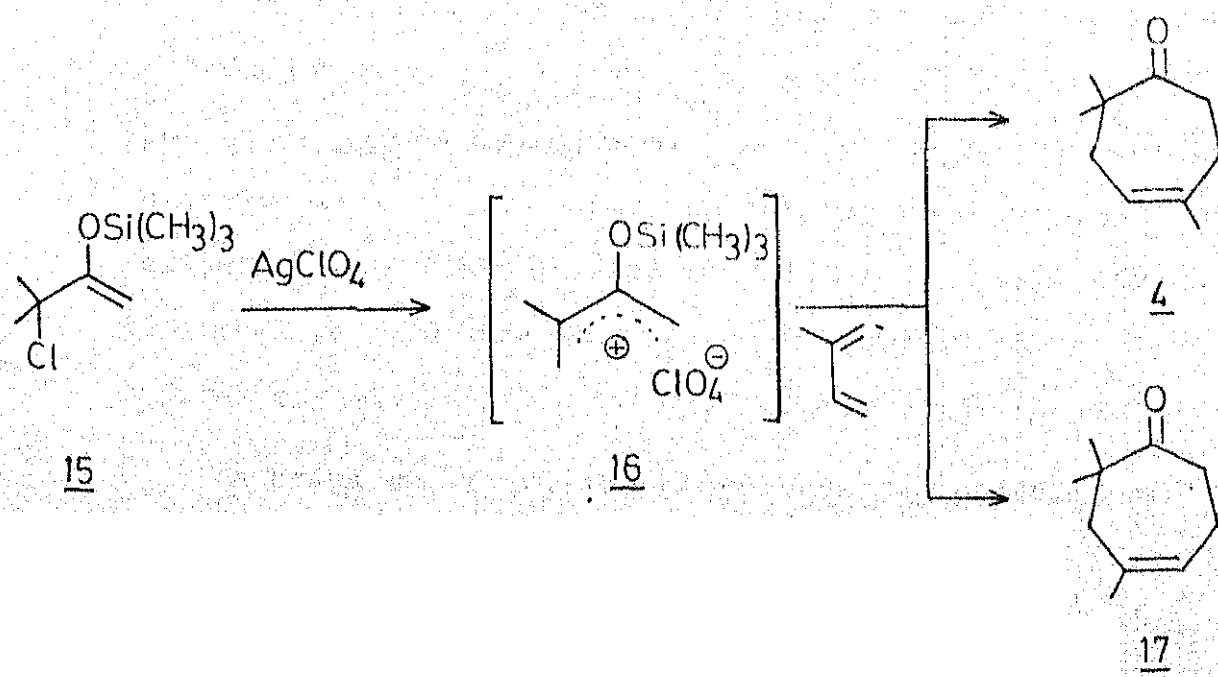
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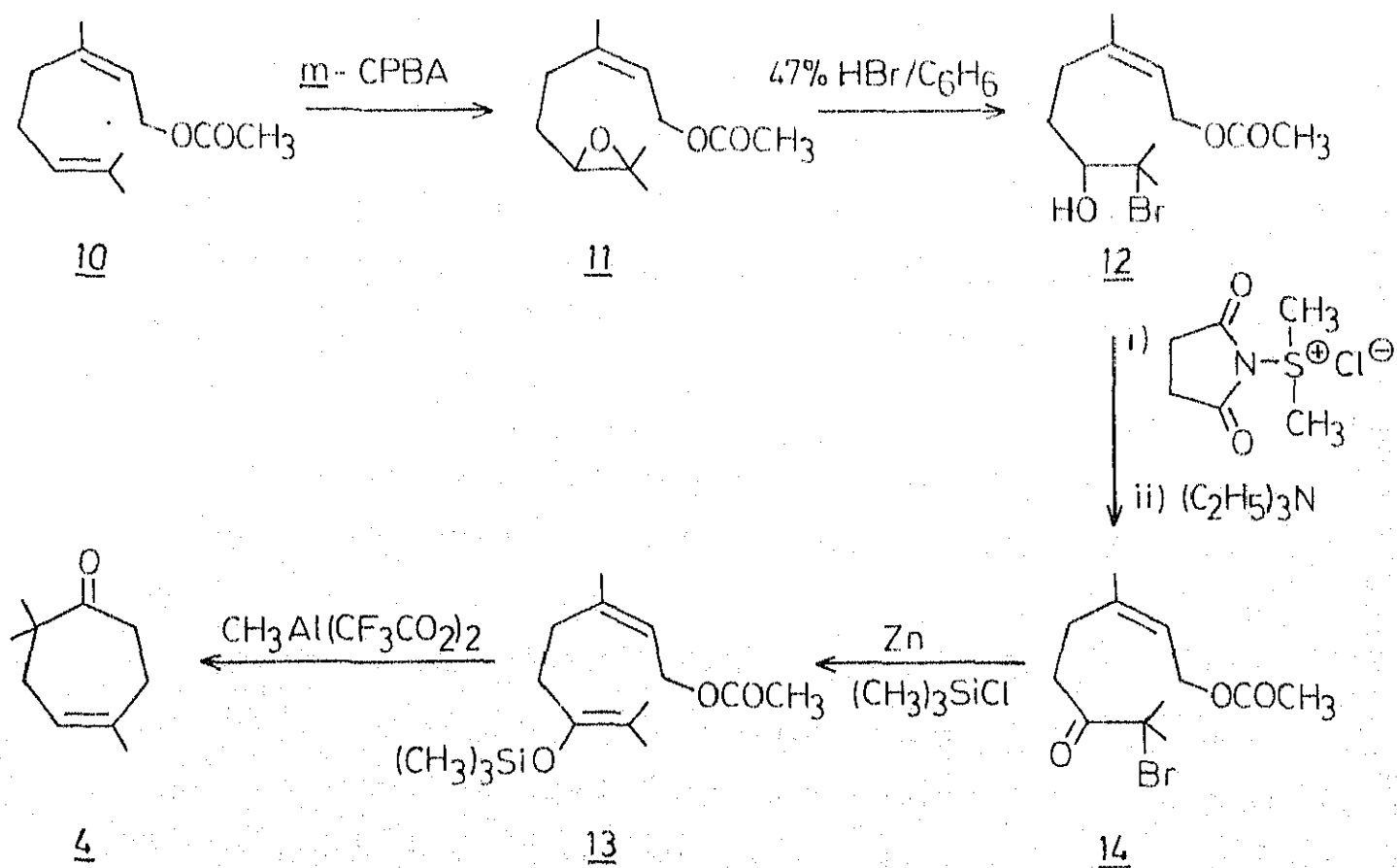
Scheme I B 3



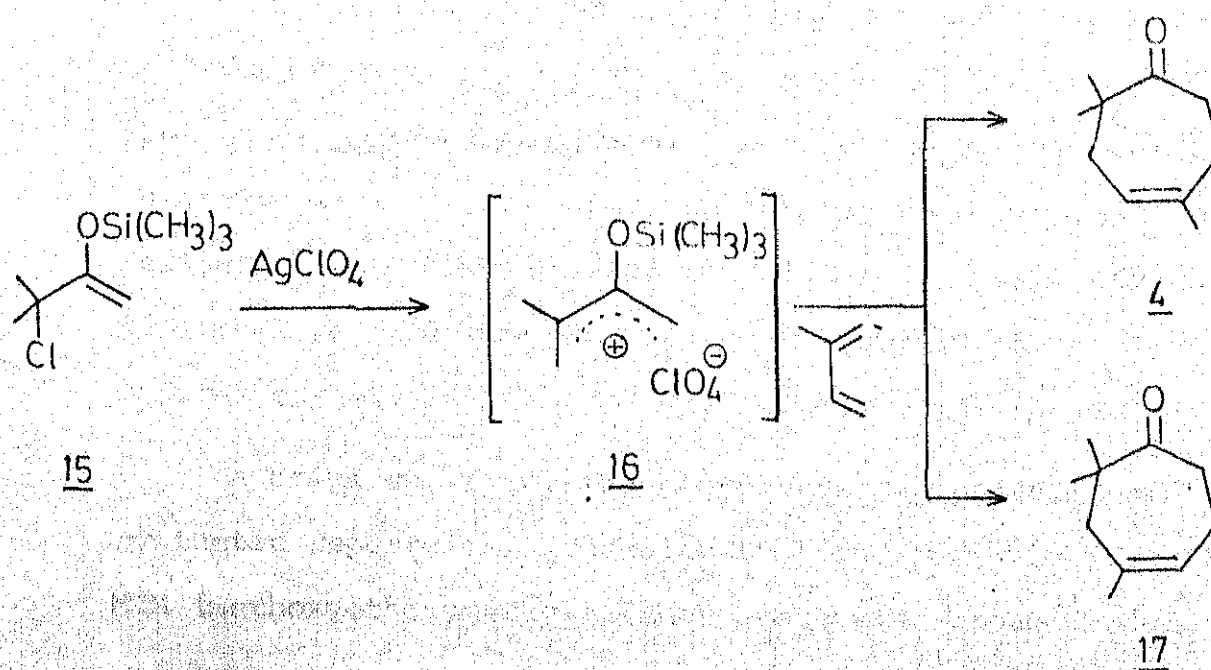
Scheme I.B.4



Scheme I B 3



Scheme I.B.4



The β,γ -unsaturated ketone, 4-methyl-3-cyclohexenone (18) has been prepared as early as in 1946 by Birch, starting from 4-methylanisole (23).²³ Later, the same compound 18 was prepared by several groups of workers, by varying the hydrolysis procedure of 1-methoxy-4-methyl-1,4-cyclohexadiene (24) to the ketone 18.²⁴⁻²⁸

The compound 23 was prepared from *p*-cresol (22) in quantitative yield by the well known procedure for methylation of phenols²⁹ and was reduced with lithium and liquid ammonia to give 24 (83%), b.p. 62-64°C (15 mm), [lit.²⁸ b.p. 128-130°C (250 mm)]. The compound 24 was hydrolysed using 10% aqueous sulphuric acid in methanol to yield the β,γ -unsaturated ketone 18 (81%), b.p. 68-69°C (18 mm), [lit.²⁸ b.p. 37-37.5°C (2.5 mm)]. The spectral data of 18 were closely similar to that reported in the literature²⁸ (Scheme I.B.6).

The compound 18 was always contaminated with some α,β -unsaturated ketone 25, under the acidic conditions in which the enol ether 24 was hydrolysed. In order to acquire reasonable quantity of very pure β,γ -unsaturated ketone 18, it was decided to explore a similar but different route, wherein the intermediate enol ether can be hydrolysed in the absence of mineral acids.

A brief survey of the protective groups available in the synthetic repertoire³⁰ revealed that the recently described MEM (methoxyethoxymethyl) ether protecting group³¹ would be

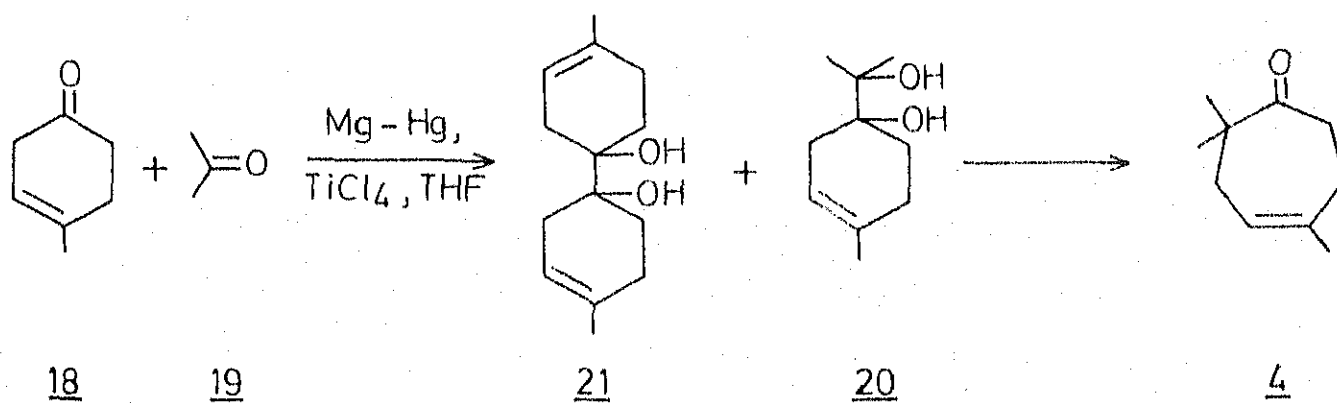
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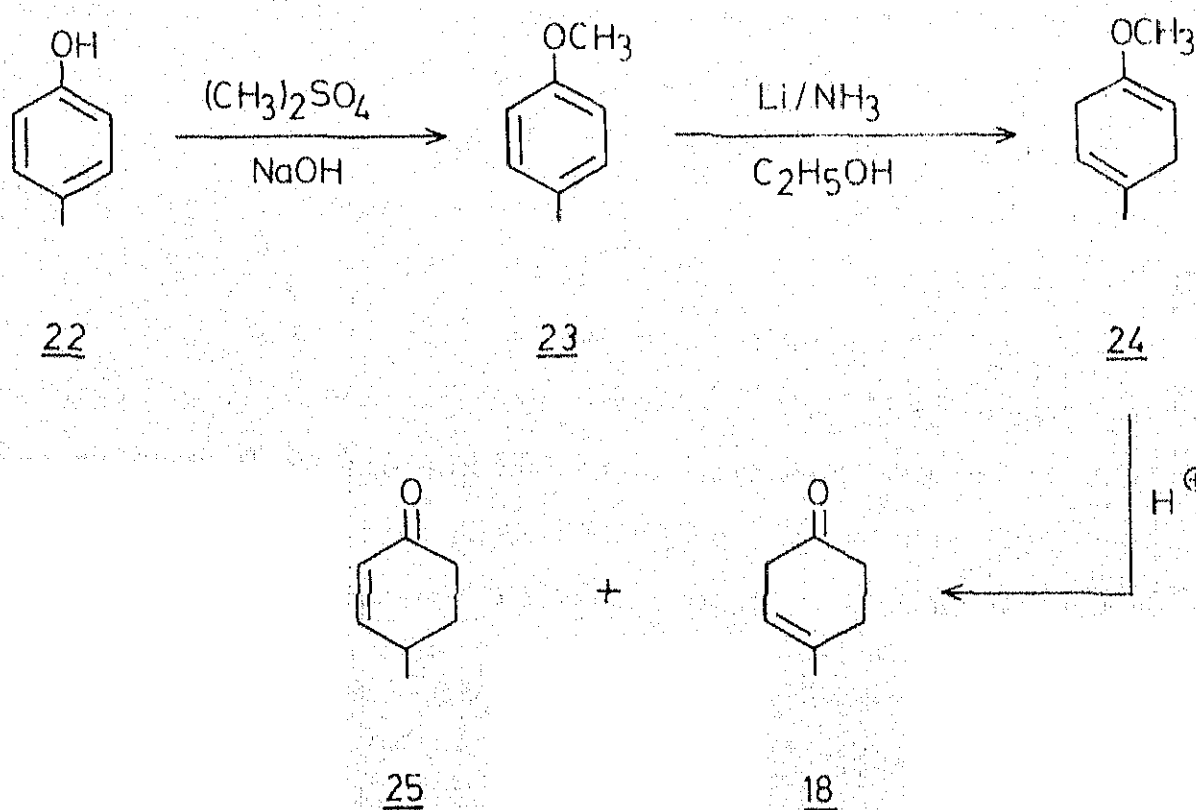
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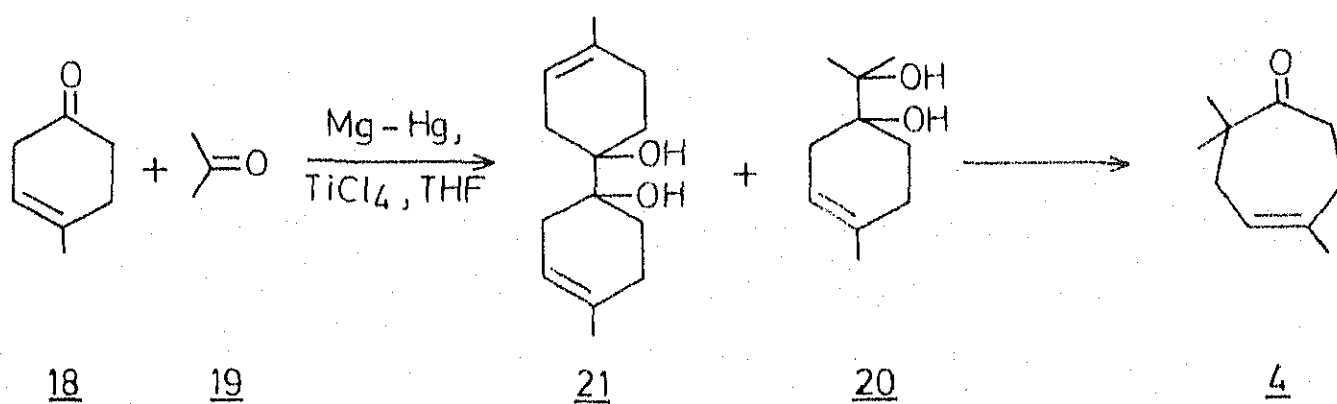
Scheme I.B.5



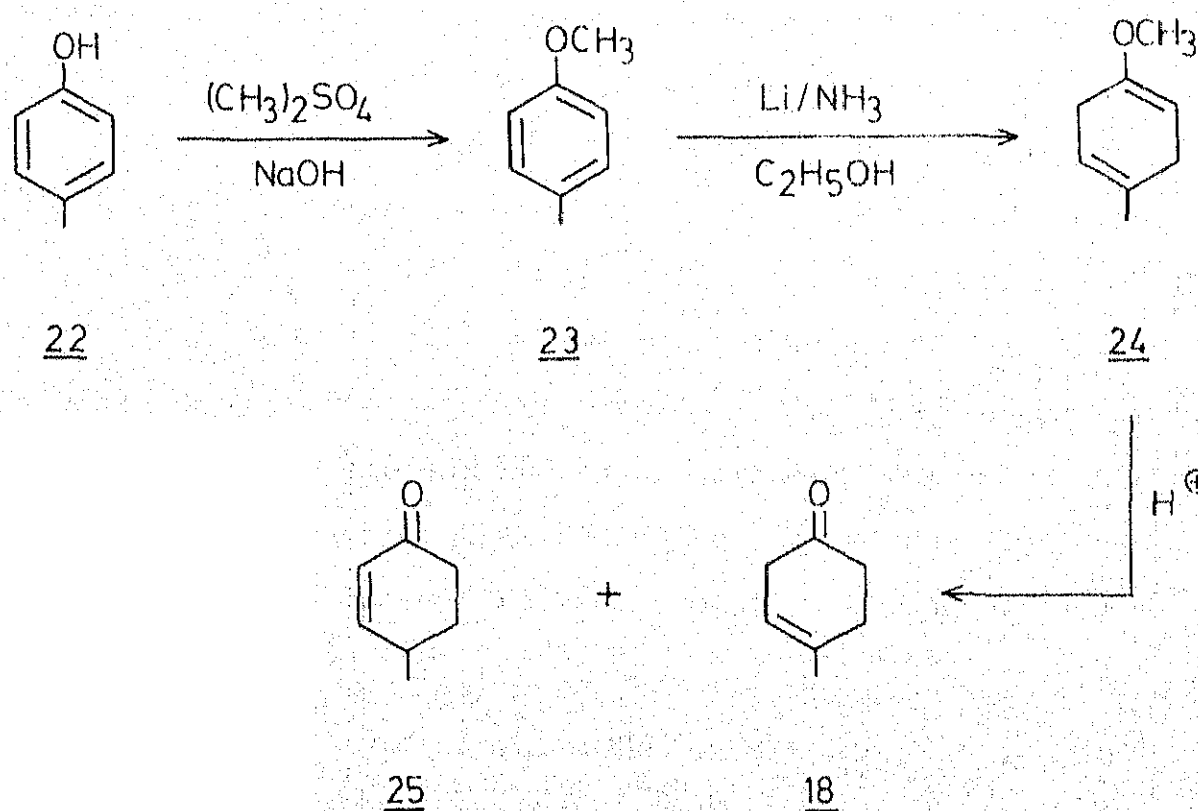
Scheme I.B.6



Scheme I.B.5



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compatible with our need. The availability of several oxygens in the protective group to complex with Lewis acids facilitates the cleavage of this ether under mild conditions using reagents such as zinc bromide and titanium tetrachloride. This prompted us to study the Birch reduction of MEM ether of p-cresol, followed by hydrolysis of the enol MEM ether with anhydrous zinc bromide (Scheme I.B.7).

The MEM chloride was prepared using a modified procedure using paraformaldehyde instead of s-trioxane as reported.³¹ The MEM ether of p-cresol was obtained by preforming the phenolate ion by treatment with sodium hydride in dry tetrahydrofuran at 0°C, followed by reaction with MEM chloride 28. The MEM ether 29, 4-methoxyethoxymethoxytoluene, was obtained in good yield (78%), b.p. 128-132°C (11 mm). The IR spectrum showed peaks characteristic of the ether linkages, at 1120, 1100 and 1000 cm^{-1} . The PMR spectrum gave a singlet at δ 2.33 (3H) corresponding to the methyl group protons and another singlet at 3.36 (3H) corresponding to the methoxy group protons. The ethylenedioxy protons showed a multiplet centred at 3.62 (4H). The methylenedioxy protons indicated a singlet at 5.23 (2H) and a multiplet appeared for the aromatic protons centred at 6.89 (4H) (Fig. I.B.1).

The lithium ammonia reduction of MEM ether 29 in the presence of ethanol as a proton source resulted in the formation of 4-methoxyethoxymethoxy-2,5-dihydrotoluene (30) in

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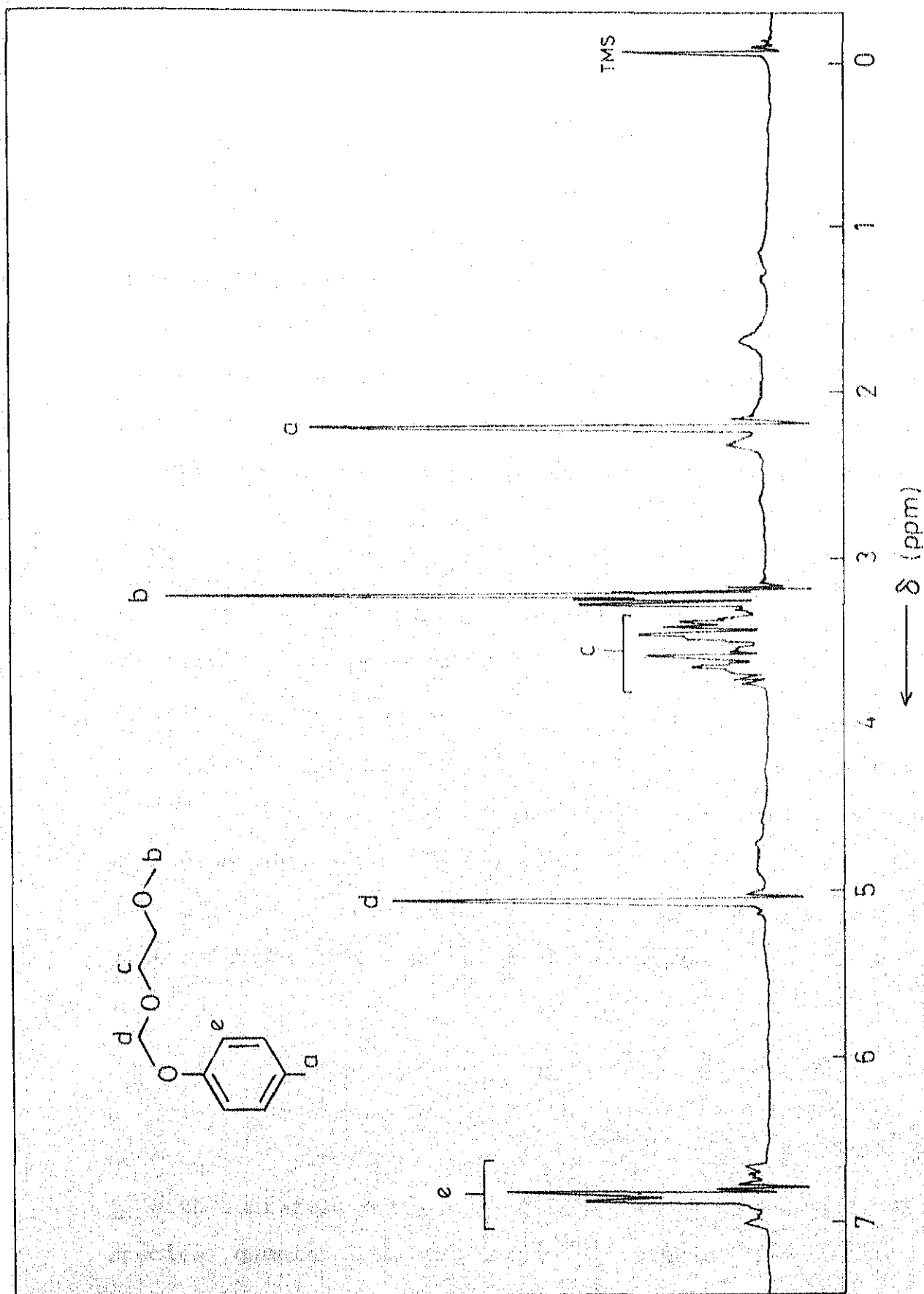


Fig. I.B.1 ^1H NMR spectrum (60 MHz) of 29.

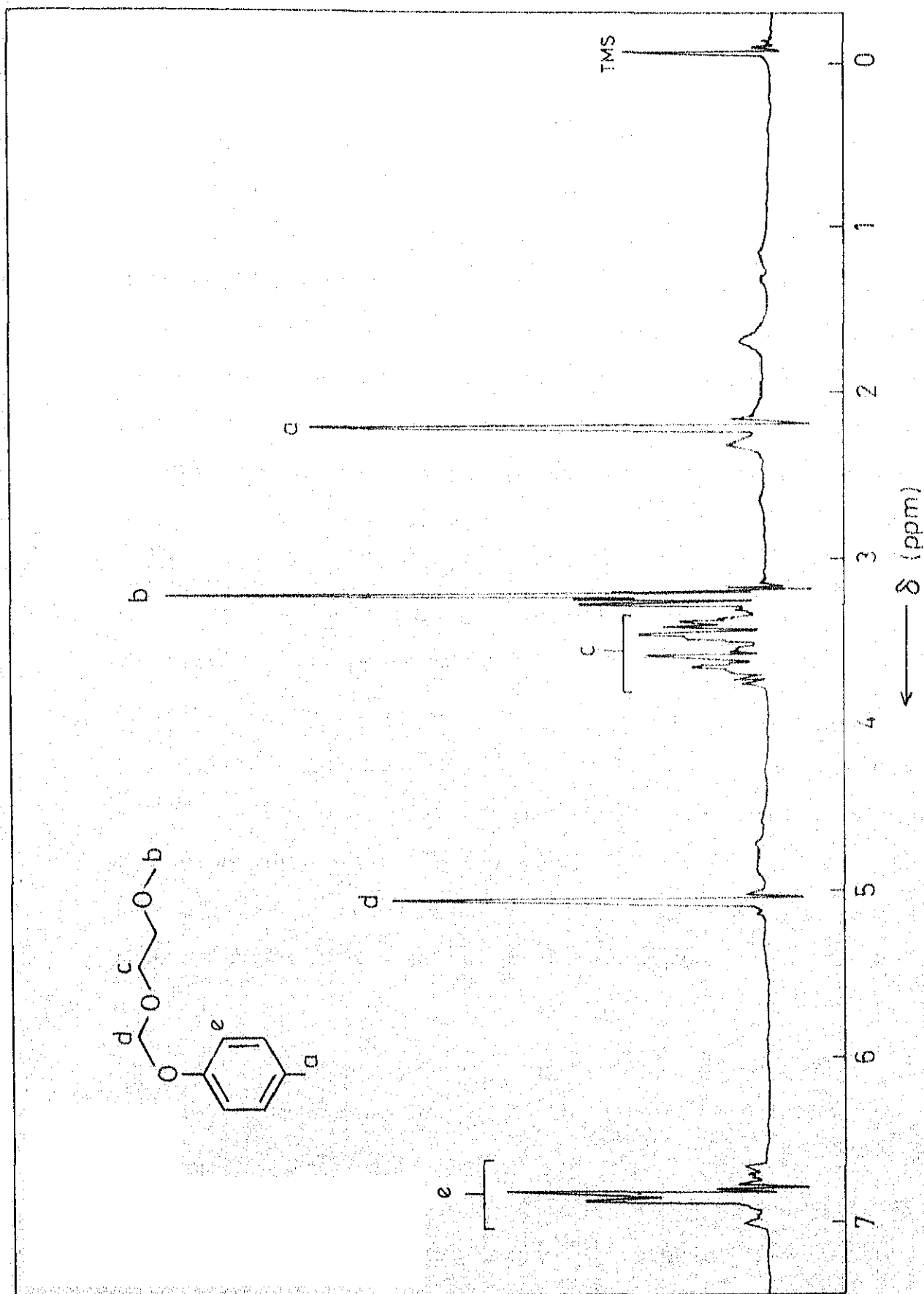


Fig. I.B.1 ¹H NMR spectrum (60 MHz) of **29**.

excellent yield (91%), b.p. 130-135°C (12 mm). The IR spectrum of 30 showed strong peaks at 1665 and 1610 cm^{-1} , indicating the presence of an enoether group. Strong absorptions at 1100 and 1060 cm^{-1} appeared due to the ether linkages. The PMR spectrum showed a slightly split singlet at δ 1.66 (3H), corresponding to the vinylic methyl group protons, a broad singlet at 2.66 (4H), due to the allylic protons and a singlet at 3.33 (3H) assigned to the methoxy group protons. The ethylenedioxy protons showed as a multiplet centred at 3.53 (3H) and the vinylic proton showed again a multiplet centred at 4.84 (1H). A singlet was indicated by methylenedioxy protons at 5.0 (2H) and a multiplet appeared at 5.33 (1H), corresponding to the vinylic protons (Fig. I.B.2).

The crucial hydrolysis of the enol ether was successfully achieved under very mild conditions by treatment with anhydrous zinc bromide (2 equivalents) in dichloromethane at room temperature. The β,γ -unsaturated ketone 18 was isolated in 80% yield without even a trace of α,β -unsaturated ketone 25 as impurity.

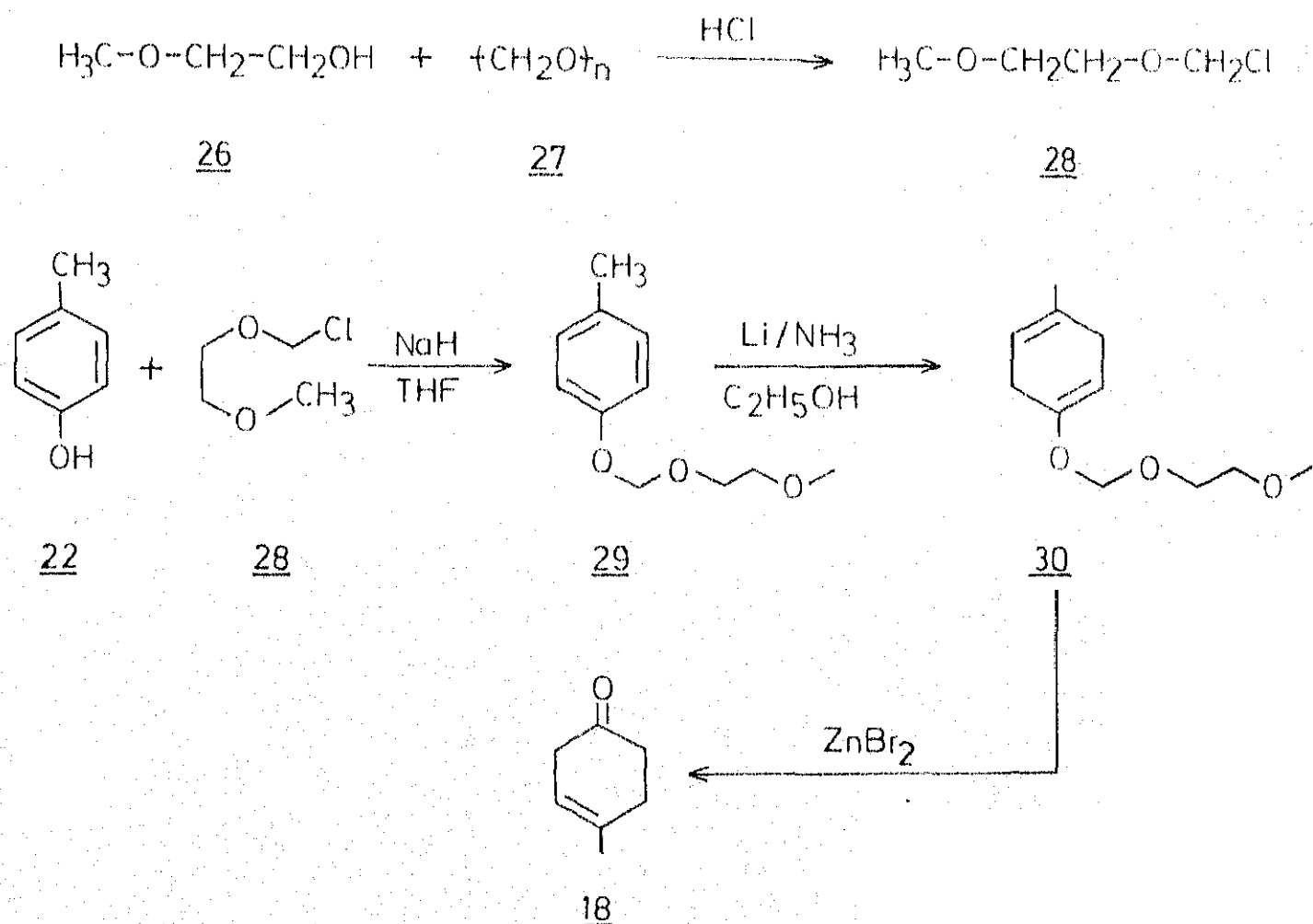
The synthesis of the unsymmetrical pinacol 20 was conveniently accomplished according to the procedure of Corey and coworkers.¹² Thus the reaction of the β,γ -unsaturated ketone 18 with four-fold excess of acetone in the presence of Ti(II) species, generated by the action of titanium tetrachloride and amalgamated magnesium in anhydrous tetrahydrofuran, under

excellent yield (91%), b.p. 130-135°C (12 mm). The IR spectrum of 30 showed strong peaks at 1665 and 1610 cm^{-1} , indicating the presence of an enoether group. Strong absorptions at 1100 and 1060 cm^{-1} appeared due to the ether linkages. The PMR spectrum showed a slightly split singlet at δ 1.66 (3H), corresponding to the vinylic methyl group protons, a broad singlet at 2.66 (4H), due to the allylic protons and a singlet at 3.33 (3H) assigned to the methoxy group protons. The ethylenedioxy protons showed as a multiplet centred at 3.53 (3H) and the vinylic proton showed again a multiplet centred at 4.84 (1H). A singlet was indicated by methylenedioxy protons at 5.0 (2H) and a multiplet appeared at 5.33 (1H), corresponding to the vinylic protons (Fig. I.B.2).

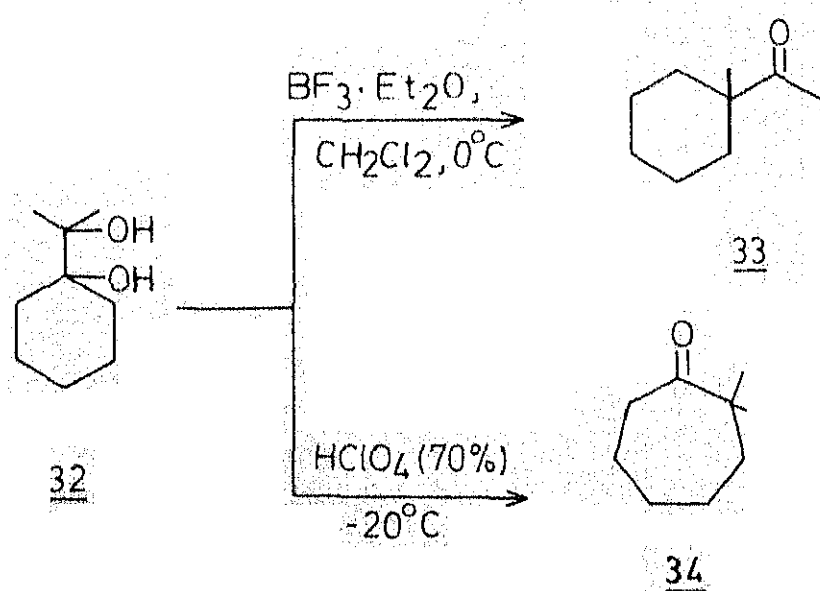
The crucial hydrolysis of the enol ether was successfully achieved under very mild conditions by treatment with anhydrous zinc bromide (2 equivalents) in dichloromethane at room temperature. The β,γ -unsaturated ketone 18 was isolated in 80% yield without even a trace of α,β -unsaturated ketone 25 as impurity.

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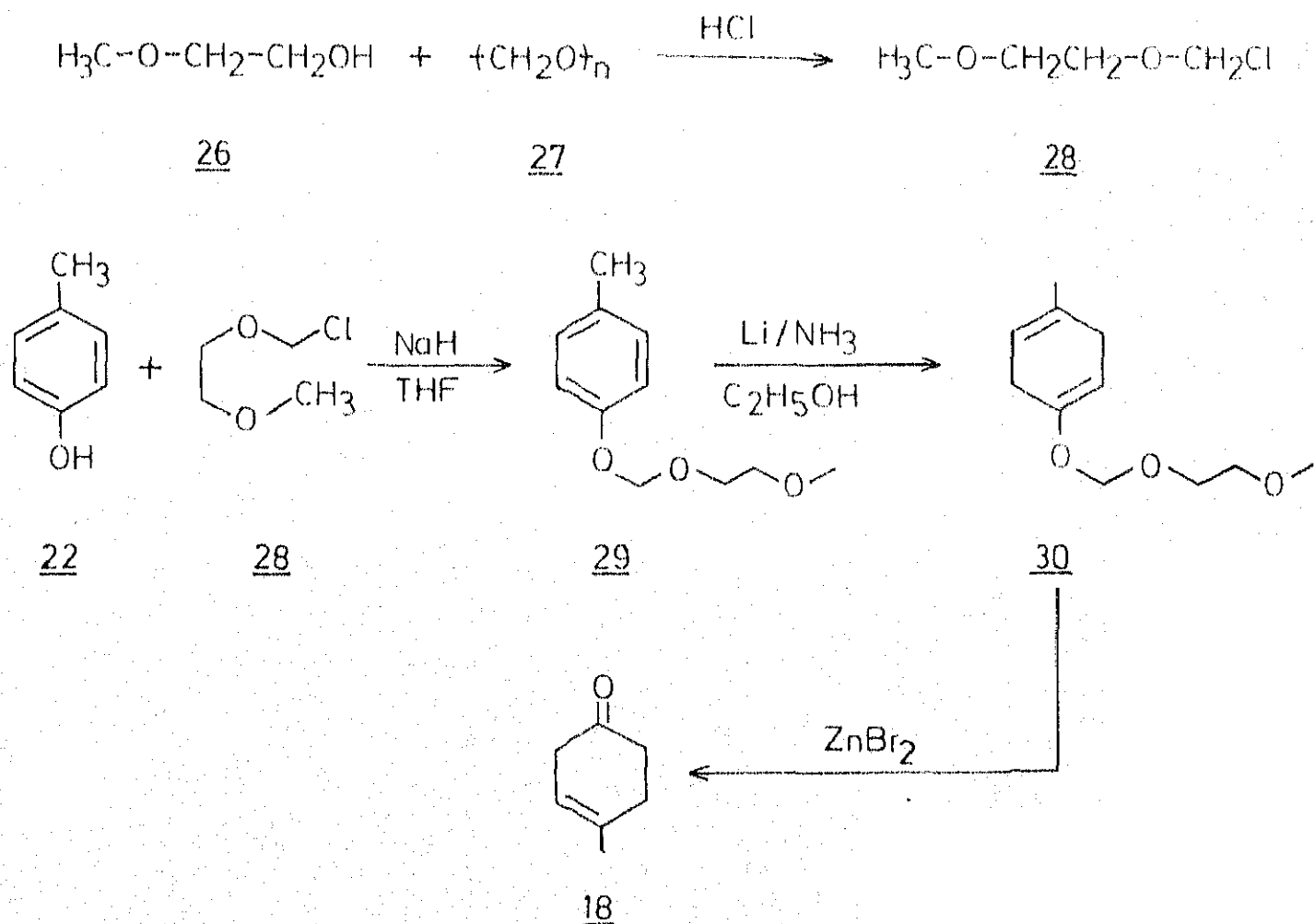
Scheme I-B.7



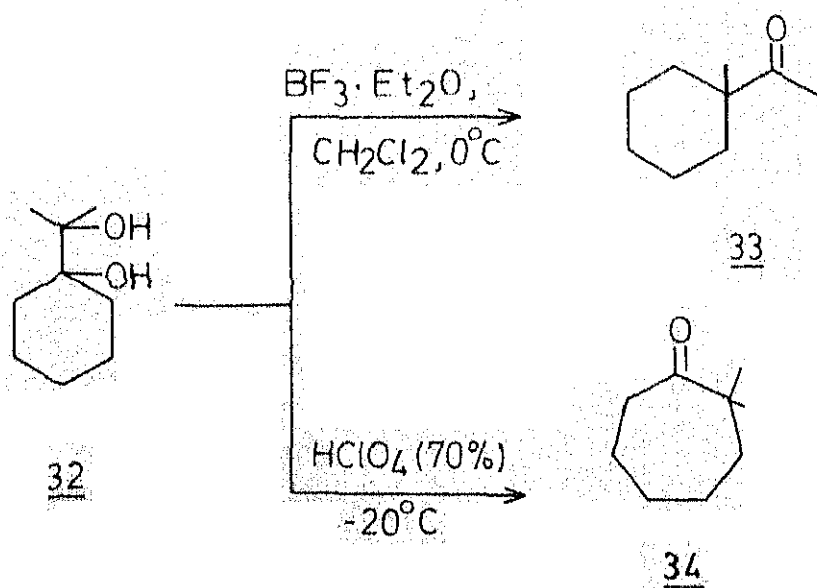
Scheme I-B.8



Scheme I.B.7



Scheme I.B.8



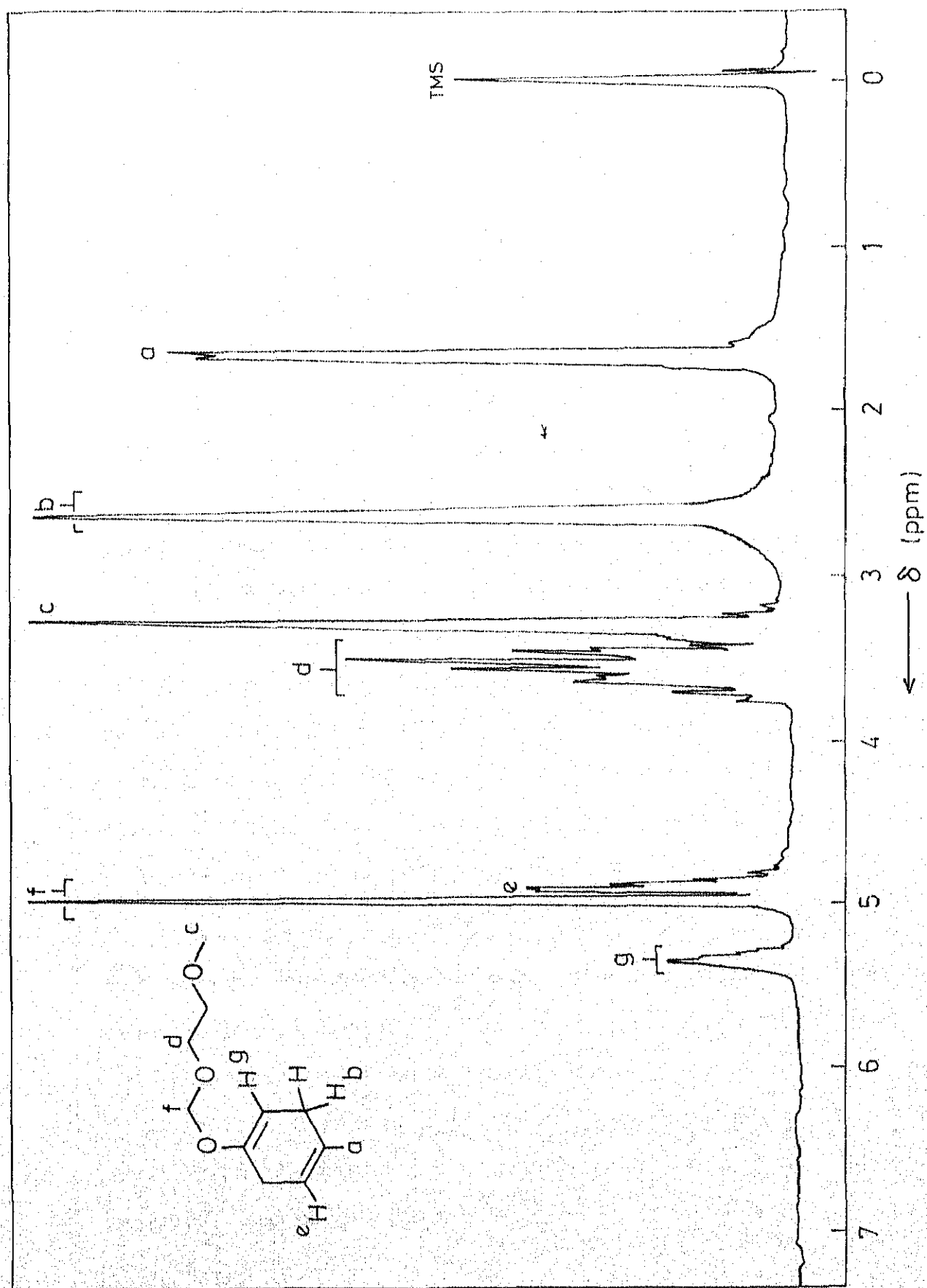


Fig. I.B.2 ^1H NMR spectrum (60 MHz) of **30**.

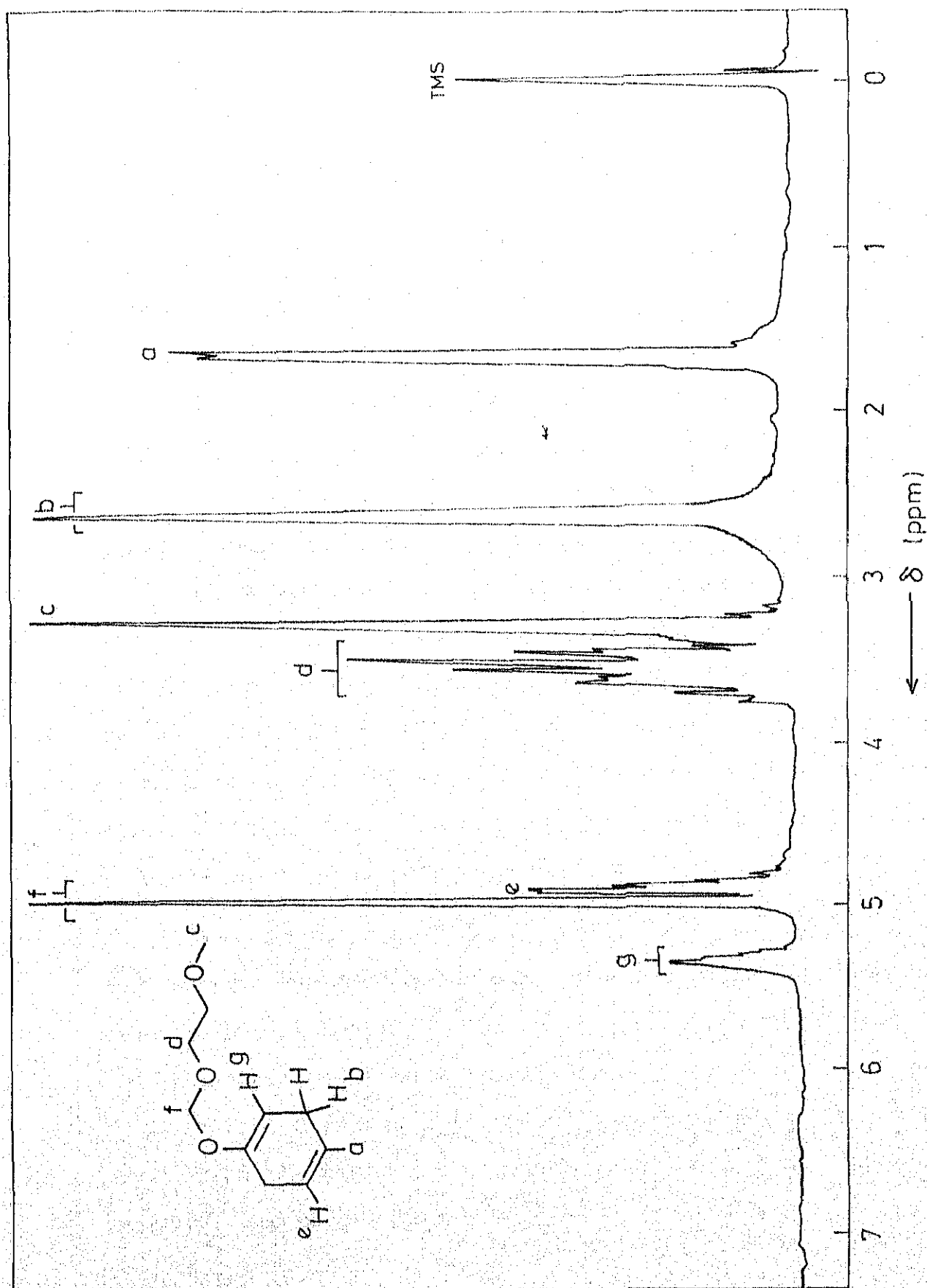


Fig. I.B.2 ^1H NMR spectrum (60 MHz) of 30.

nitrogen atmosphere, afforded a mixture of three compounds, viz. unsymmetrical pinacol 20, symmetrical pinacol 21 and acetone pinacol. The unsymmetrical pinacol, 1-(2'-hydroxypropyl)-4-methyl-3-cyclohexenol (20) was isolated by flash column chromatography in 57% yield, as a colourless oil. The IR spectrum of 20 showed a broad absorption at 3425 cm^{-1} characteristic of the hydroxyl group. The PMR spectrum indicated two very closely situated singlets at $\delta 1.2$ (3H) and 1.22 (3H) which can be assigned to the gem-dimethyl group protons. The vinylic methyl group protons appeared as a slightly split singlet at $\delta 1.69$ (3H). The complex multiplet centred at 1.95 (8H) can be assigned to the methylene protons and two hydroxyl group protons (D_2O exchangeable). The vinylic proton appeared as a broad signal centred at 5.32 (1H) (Fig. I.B.3). The mass spectrum showed a peak at m/e 152.1 ($\text{M}^+ - 18$). A small amount of the symmetrical pinacol 21 was also isolated (5%), m.p. $94-95^\circ\text{C}$, which was characterized based on the spectral data.

The reductive coupling reaction to obtain the unsymmetrical pinacol was done under carefully controlled conditions. The best yield was obtained when the reaction was carried out below -10°C and the reaction mixture worked up as soon as the starting material disappears in the tlc analysis (0.75 h). Recent studies on the pinacolic coupling reaction by Mundy et al. support our observation.³²

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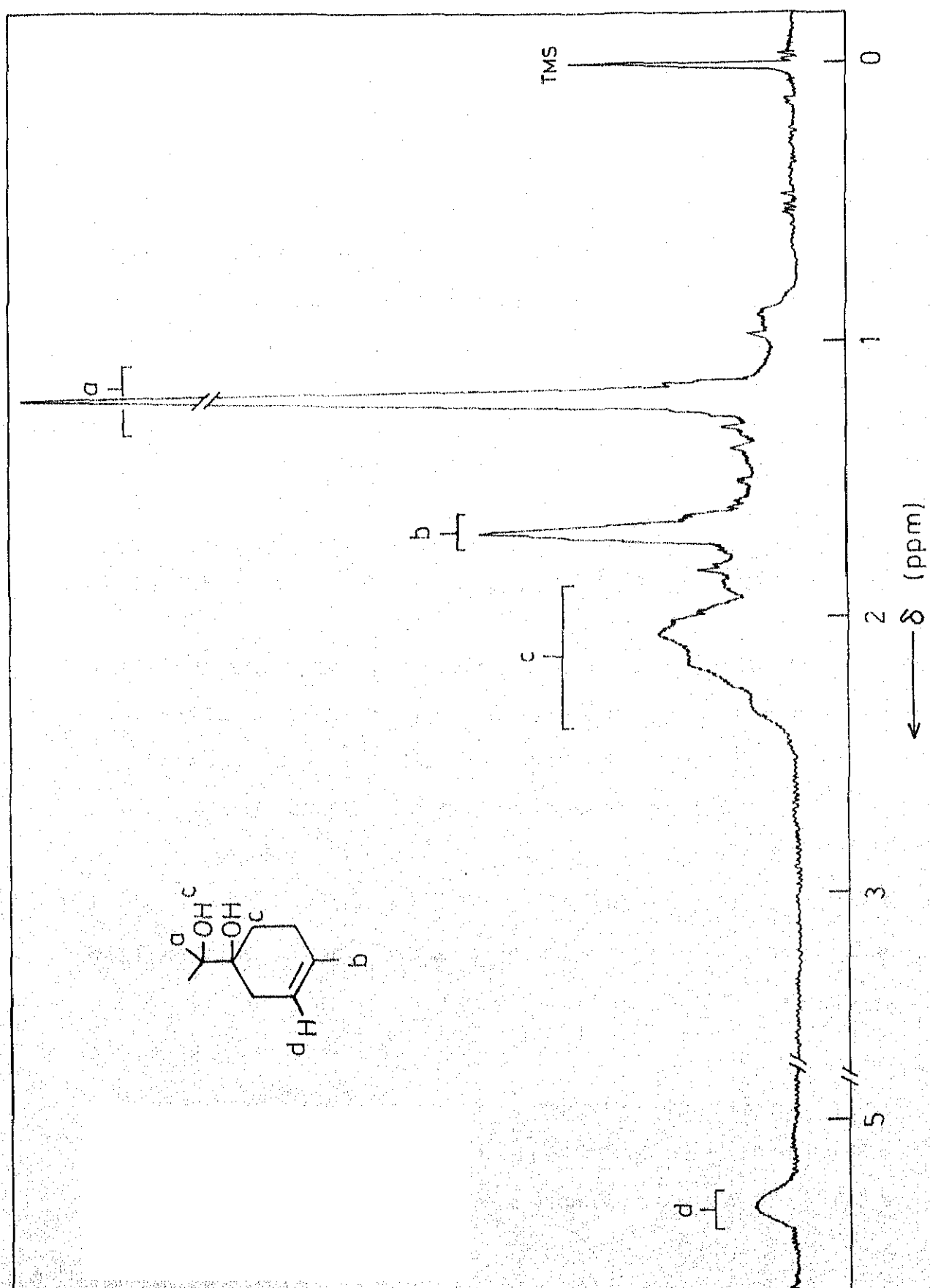


Fig. I-B-3 ^1H NMR spectrum (100 MHz) of 20.

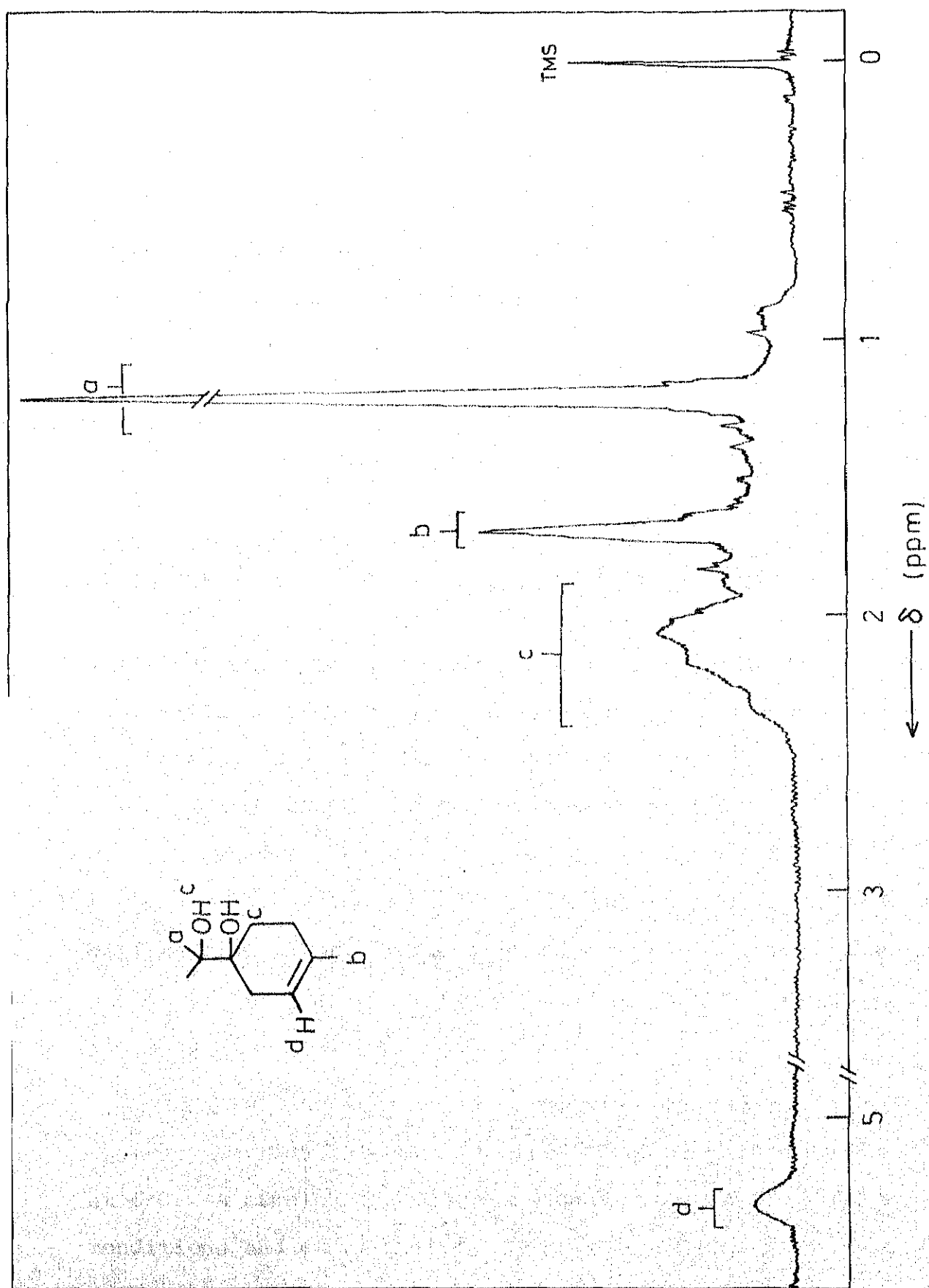
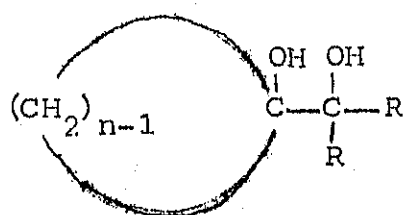


Fig. I-B-3 ^1H NMR spectrum (100 MHz) of 20.

According to the strategy planned, the pinacol rearrangement of the unsymmetrical pinacol 20 would lead to Karahanaenone (4). Dilute or concentrated sulphuric acid has been used for pinacol rearrangements for a long time.³³ Meerwin has rearranged a series of glycols of the general formula 31 to get the ring expansion products using concentrated sulphuric acid.³⁴

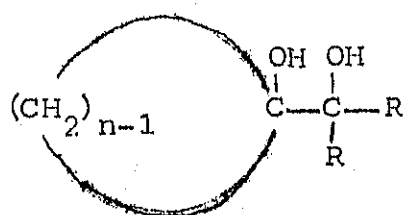
31

- a) $n = 6$; $R = \text{CH}_3$
- b) $n = 6$; $R = \text{C}_2\text{H}_5$
- c) $n = 5$; $R = \text{CH}_3$
- d) $n = 5$; $R = \text{C}_2\text{H}_5$

The ring size effects in the pinacol rearrangement have also been investigated, wherein it was found that when the reactions were conducted at 0°C in concentrated sulphuric acid, no elimination was observed and good yields of rearrangement products were obtained.³⁵ During the studies of the applicability of the pinacol rearrangement for the synthesis of spiro ketones of various ring sizes, it has been observed again, that the highest yields of the spiranones were obtained with concentrated sulphuric acid.³⁶

With a view to effecting the ring expansion, we treated the unsymmetrical pinacol 20 with concentrated sulphuric acid at 0°C . A complex mixture of products was obtained under these conditions and other methods of bringing about this rearrangement had to be looked into.

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Corey and coworkers have demonstrated the utility of unsymmetrical pinacols as useful synthetic intermediates.¹² They have found two different trends in the rearrangement of the unsymmetrical pinacol 32. When 1-(2'-hydroxypropyl)cyclohexanol (32) was treated with boron trifluoride etherate in dichloromethane at 0°C, the methyl group was found to migrate to give 33 and treatment with perchloric acid (70%) at -20°C, resulted in ring expansion yielding 2,2-dimethylcycloheptanone (34), as depicted in Scheme I.B.8. When the unsymmetrical pinacol 20 was subjected to perchloric acid treatment, it again gave rather a complex mixture of products. Failure to achieve the desired ring expansion using mineral acids can be attributed to the presence of the double bond in 20. The easy protonation of the double bond in the presence of acid might have been the major competing reaction.

Unsuccessful attempts to effect the crucial ring expansion of the key intermediate 20, prompted us to explore the possibility of effecting such a rearrangement by the use of Lewis acids. Ferric chloride adsorbed on chromatographic silica gel has been found to be effective for dehydration of alcohols as well as for pinacol and acyloin type rearrangements.³⁷ Therefore, we treated the unsymmetrical pinacol 20 with ferric chloride on silica gel, prepared by the reported procedure.³⁷ The compound 20 was found to remain inert towards this Lewis acid on the solid support. The unsymmetrical pinacol 20 was

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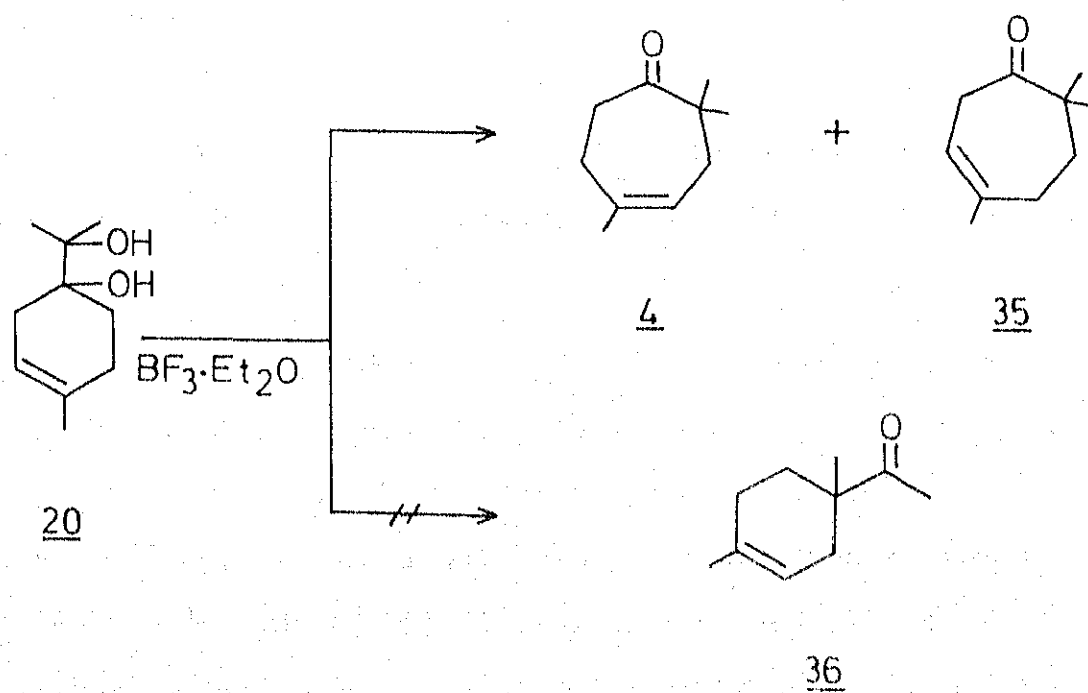
also subjected to treatment with titanium tetrachloride in solvents such as tetrahydrofuran and methylene chloride at 0°C and lower, which did not yield any useful product.

At this point, we decided to investigate the behaviour of the unsymmetrical pinacol 20 towards boron trifluoride etherate. Boron trifluoride etherate has been effectively used in the synthesis of spiroketones starting from 1,1'-bicyclic diols.³⁶ Although it is well-known to bring about ring expansion by pinacol rearrangement, we were hesitant to use this reagent earlier on the basis of the reports by Corey et al.¹² However, when the unsymmetrical pinacol 20 was exposed to boron trifluoride etherate in dichloromethane at 0°C for 12 h, a mixture of two products was obtained in about 82% yield (Scheme I.B.9). The GC-MS analysis (10% SE-30, 140°C) indicated the presence of two components with molecular ion peaks at m/e 152 (M^+), in the ratio of 70:30. The crude product mixture was purified by preparative gas chromatography (10% SE-30, 140°C) to yield Karahanaenone (4, 57%), as a pleasant smelling oil, (semicarbazone, m.p. 164-168°C).¹⁶ The spectral data were closely similar to that reported for the natural product.¹⁵ The IR spectrum showed an absorption at 1710 cm^{-1} indicative of the carbonyl group. The PMR spectrum showed a sharp singlet at δ 1.08 (6H) corresponding to the gem-dimethyl group protons and another slightly split singlet at 1.67 (3H) due to the vinylic methyl group protons. The methylene protons showed as a broad multiplet

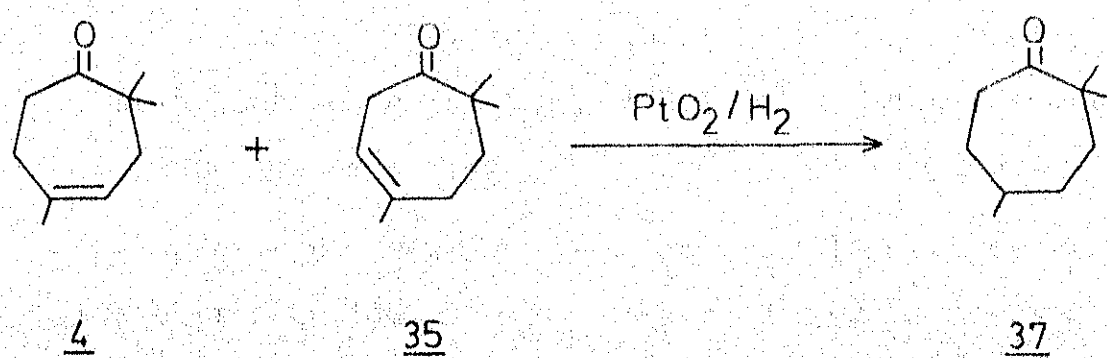
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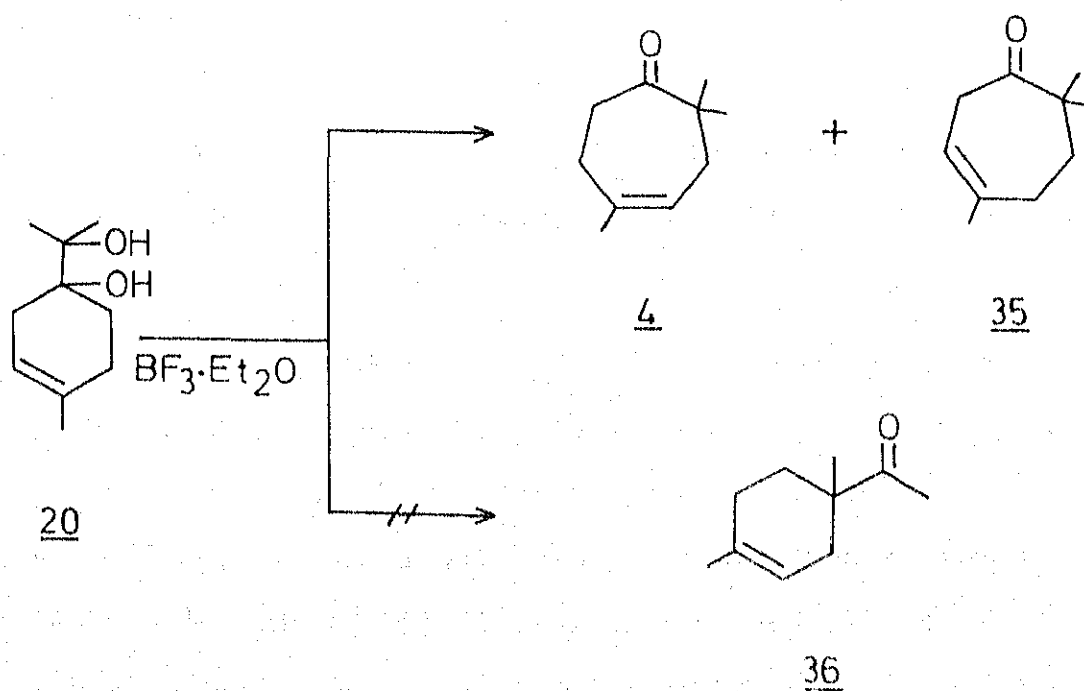
Scheme I.B.9



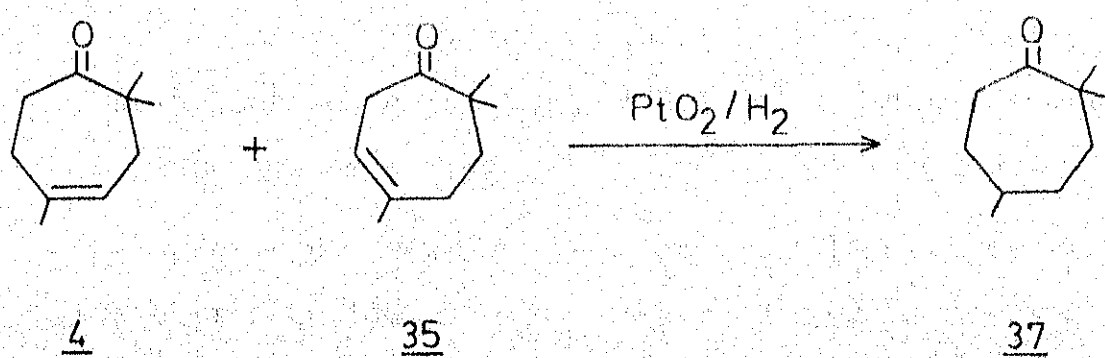
Scheme I.B.10



Scheme I.B.9



Scheme I.B.10



centred at 2.25 (4H) and a broad triplet at 2.74 (2H, $J = 7$ Hz). The vinylic proton appeared as a broad signal at 5.5 (1H) (Fig. I.B.4). The mass spectrum indicated the molecular ion peak at m/e 152.1 (M^+). Other important fragments in the spectrum were at m/e 137, 109, 97, 95, 81, 79, 70, 69, 67, 55, 53, 43, 41, identical to those reported for the natural terpene.¹⁵

The minor product 35 (24%) obtained from the preparative gas chromatography was characterized to be the isomer of Karahanaenone. The IR spectrum showed a strong absorption at 1710 cm^{-1} typical of a keto group. The PMR spectrum showed a sharp singlet at δ 1.12 (6H) which can be assigned to the gem-dimethyl group protons and another singlet at 1.66 (3H) corresponding to the vinylic methyl protons. The methylene protons showed two multiplets centred at 1.88 (2H) and 2.24 (2H), respectively. A complex doublet was indicated by the allylic methylene protons, adjacent to the carbonyl group, at δ 3.18 (2H). The vinylic proton appeared as a complex multiplet centred at 5.32 (1H) (Fig. I.B.5). The mass spectrum showed a molecular ion peak at m/e 152.1 (M^+). Other important fragments were at m/e 124, 109, 95, 81, 67, 56 and 53.

In order to prove that the two compounds obtained in the boron trifluoride etherate catalysed rearrangement of the unsymmetrical pinacol 20 differ just in the position of the double bond, a hydrogenation was carried out at atmospheric pressure, on the crude reaction product in the presence of platinum oxide

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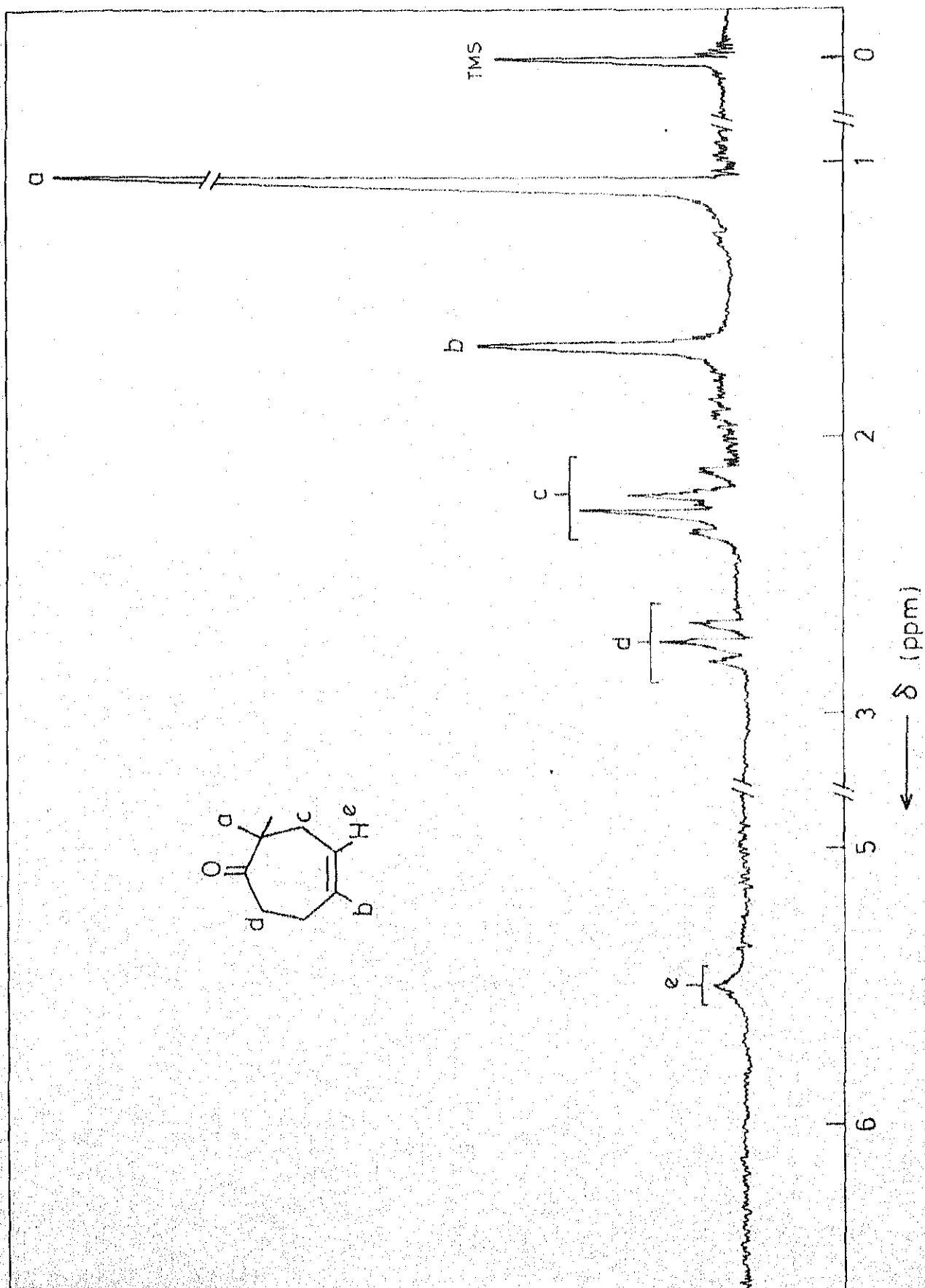


Fig. I.B.4 ^1H NMR spectrum (100 MHz) of 4.

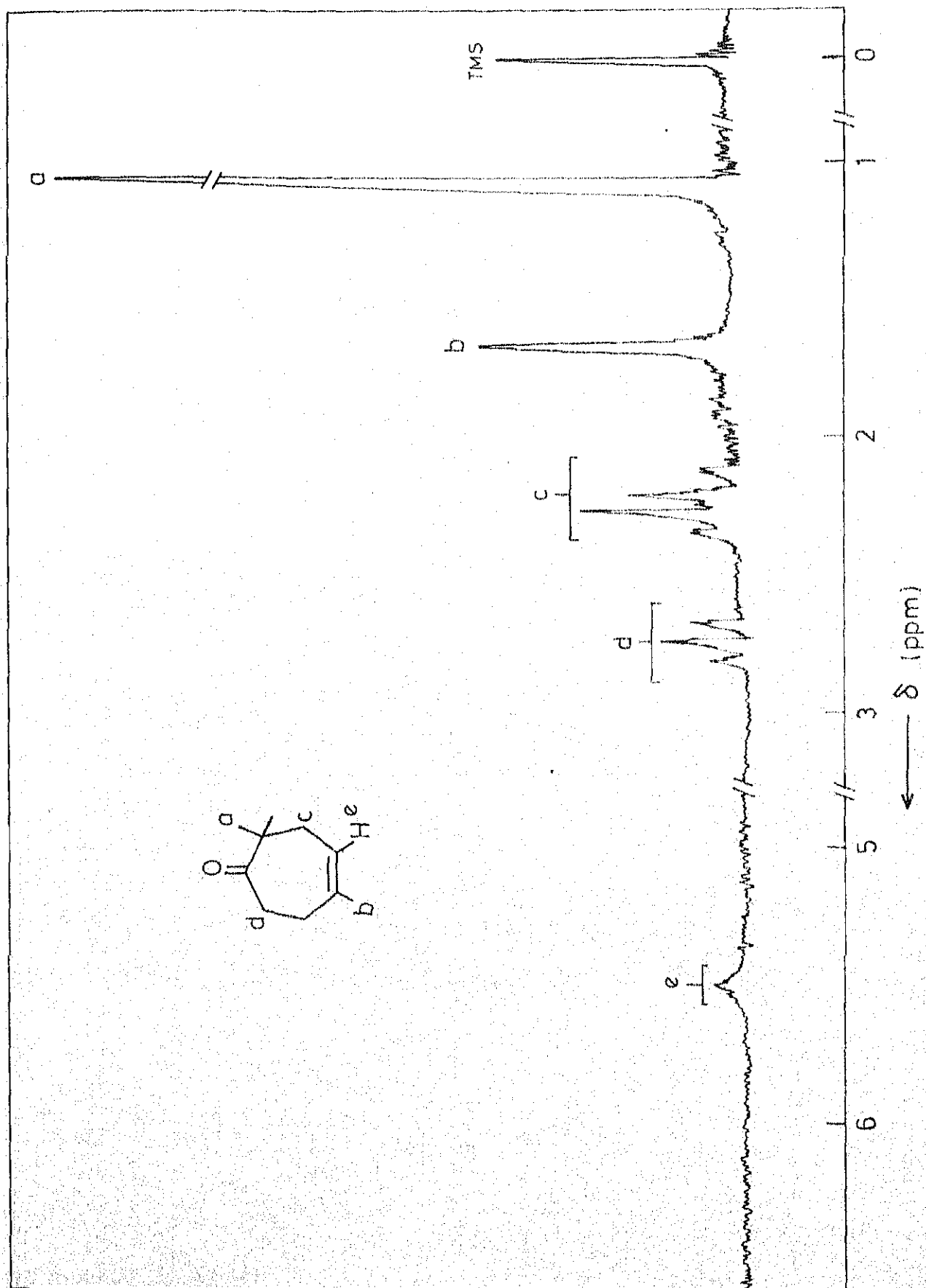


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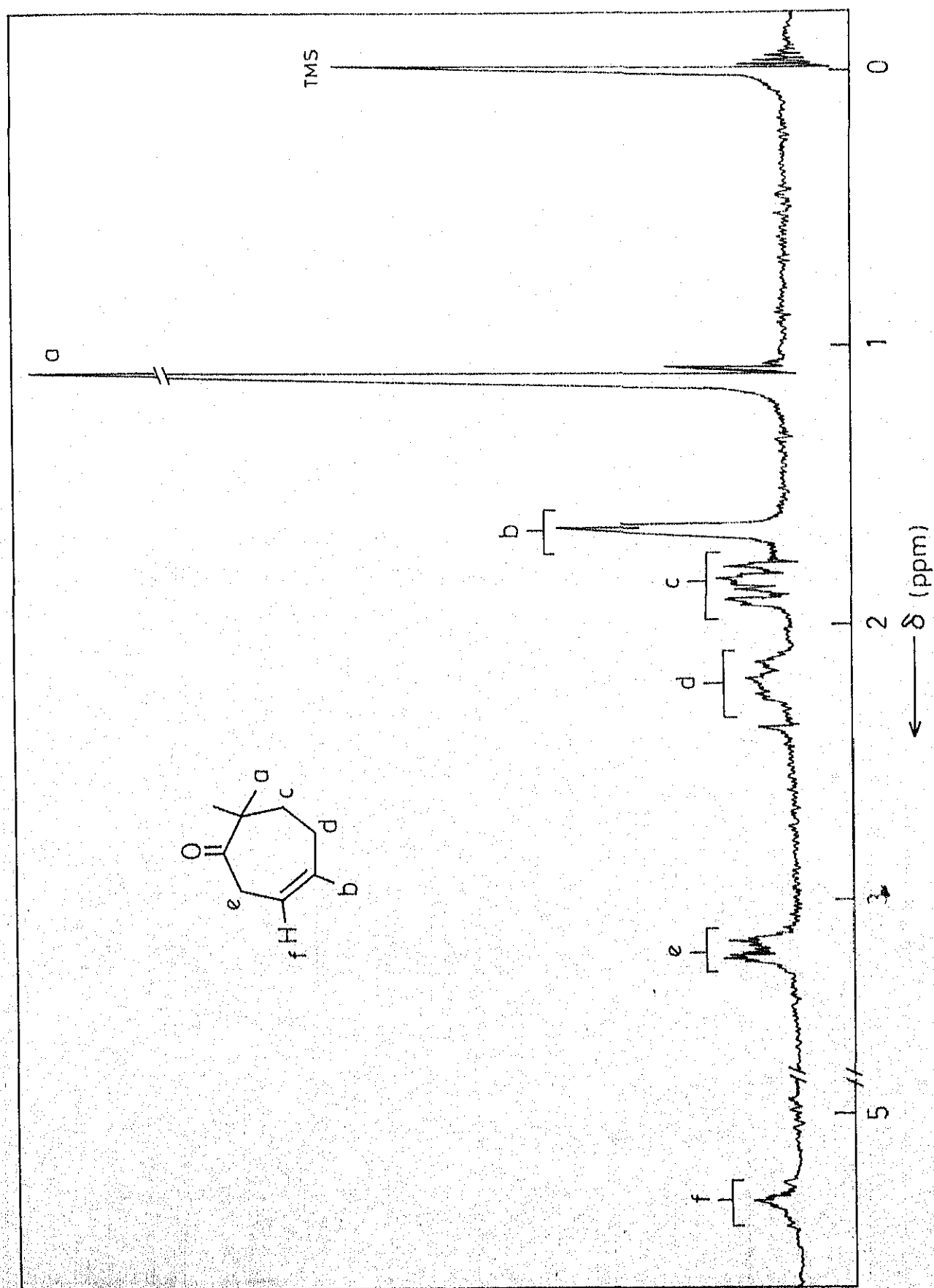


Fig. I-B-5 ^1H NMR spectrum (100 MHz) of 35.

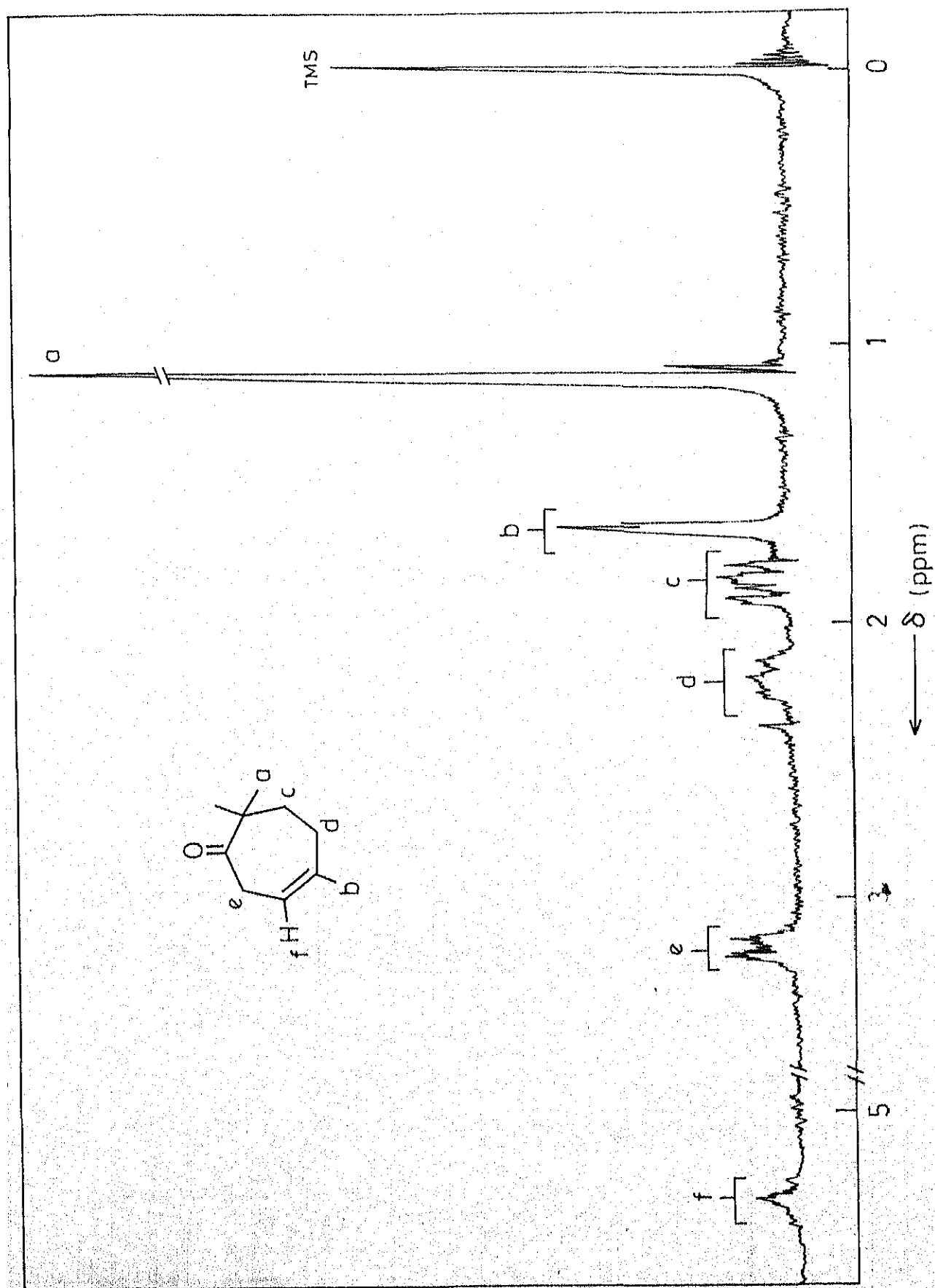


Fig. I.B.5 ^1H NMR spectrum (100 MHz) of 35.

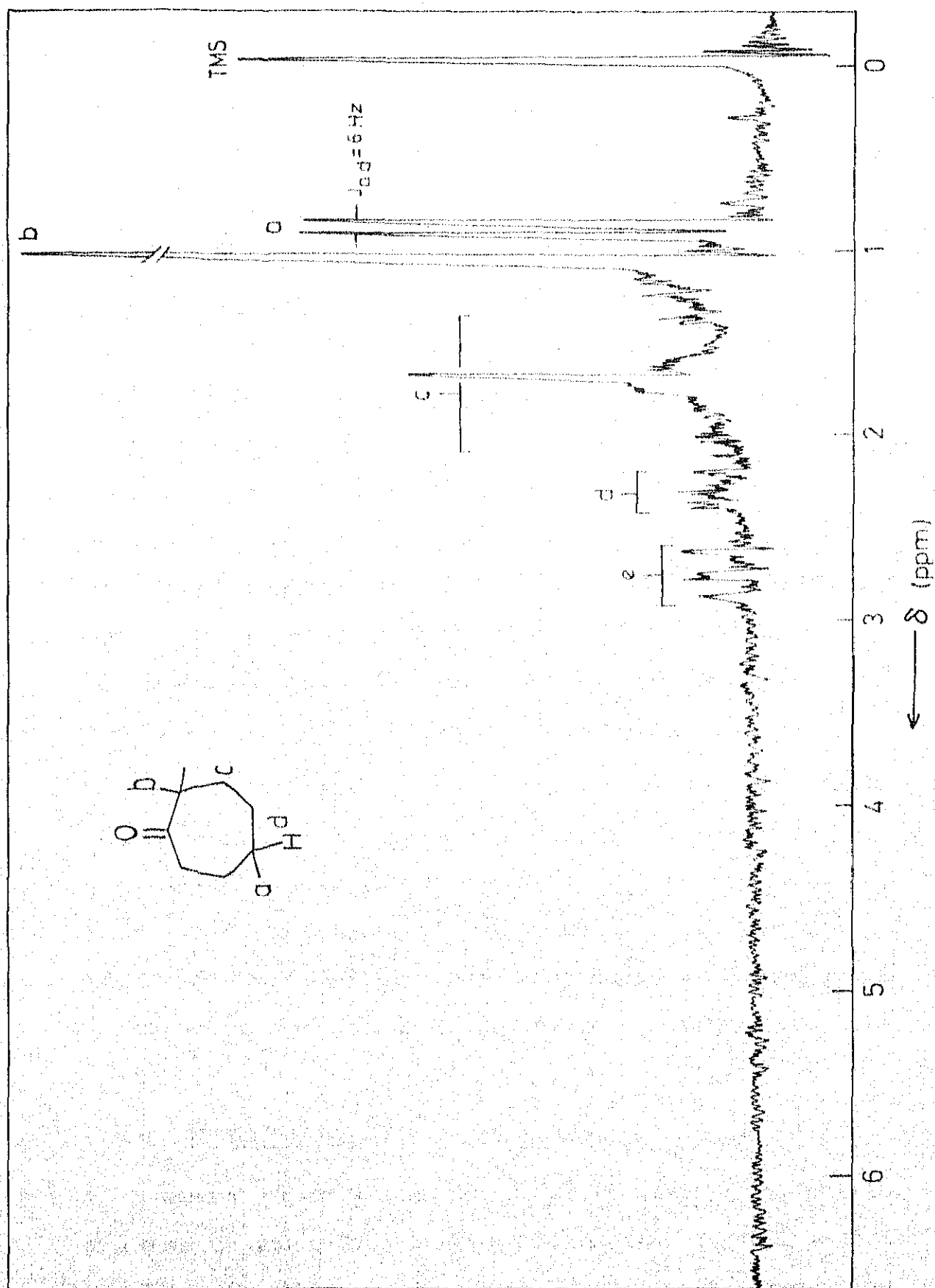


Fig. I.B.6 ^1H NMR spectrum (90 MHz) of 37.

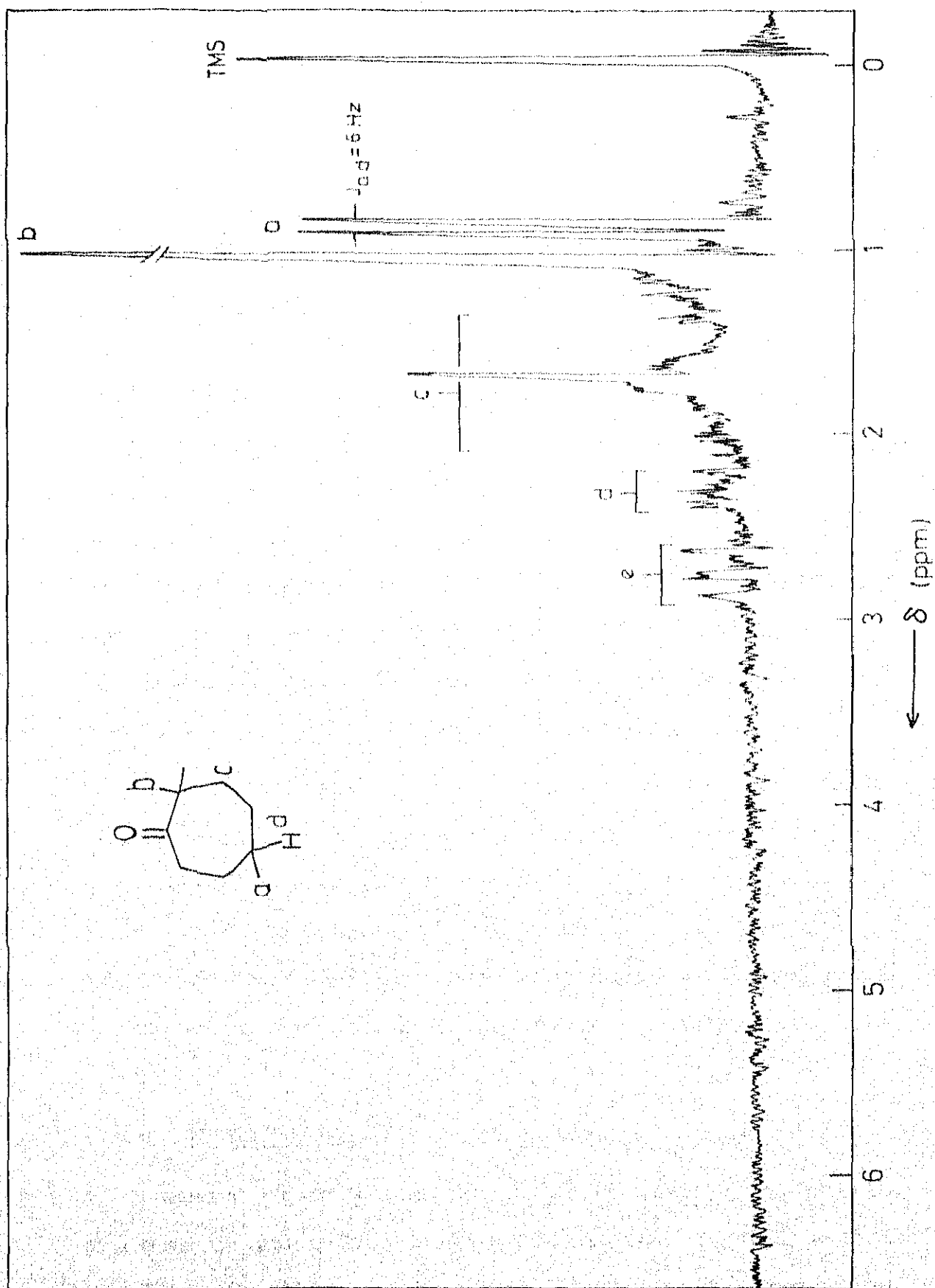


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in ethyl acetate. The hydrogenation yielded a single product (95%), the GC analysis (10% SE-30, 140°C) of which showed it to be 98% pure (Scheme I.B.10). The compound was identified to be dihydrokarakahanaenone (37). The spectral data were closely similar to that reported.^{15a} The IR spectrum showed a strong carbonyl absorption at 1700 cm^{-1} . The PMR spectrum indicated a doublet at δ 0.95 (3H, $J = 6\text{ Hz}$), attributed to the methyl group protons. A sharp singlet at 1.06 (6H) can be assigned to the gem-dimethyl group protons. The methylene protons appeared as a multiplet centred at 1.64 (6H) and the methylene protons adjacent to the keto group showed a multiplet at 2.74 (2H). The methine proton appeared as a multiplet centred at 2.28 (1H) (Fig. I.B.6). The mass spectrum showed the molecular ion peak at m/e 154.1 (M^+), thereby confirming it to be the dihydroderivative of 4.

It is of interest to note that the boron trifluoride etherate catalysed ring expansion of the unsymmetrical pinacol 20 did not give rise to any of the methyl ketone 36, although methyl ketones of this type were the major products under similar conditions.¹² Mention may be made here that Karahanaenone (4) was not as unstable to Lewis acids as was reported in the literature.¹⁸

I.B.4 EXPERIMENTAL

General procedures adopted for the reactions, purification of reagents and solvents were the same as are indicated in I.A.4. Absolute ethanol was prepared by distilling the rectified spirit

in ethyl acetate. The hydrogenation yielded a single product (95%), the GC analysis (10% SE-30, 140°C) of which showed it to be 98% pure (Scheme I.B.10). The compound was identified to be dihydrokarakahanaenone (37). The spectral data were closely similar to that reported.^{15a} The IR spectrum showed a strong carbonyl absorption at 1700 cm^{-1} . The PMR spectrum indicated a doublet at δ 0.95 (3H, $J = 6\text{ Hz}$), attributed to the methyl group protons. A sharp singlet at 1.06 (6H) can be assigned to the gem-dimethyl group protons. The methylene protons appeared as a multiplet centred at 1.64 (6H) and the methylene protons adjacent to the keto group showed a multiplet at 2.74 (2H). The methine proton appeared as a multiplet centred at 2.28 (1H) (Fig. I.B.6). The mass spectrum showed the molecular ion peak at m/e 154.1 (M^+), thereby confirming it to be the dihydroderivative of 4.

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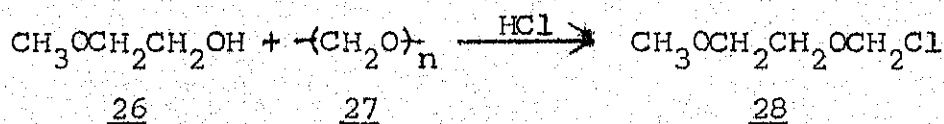
from sodium followed by magnesium ethoxide. Anhydrous liquid ammonia was obtained by distillation from sodium. Magnesium turnings were cleaned by washing with dilute hydrochloric acid, followed by distilled water, until the washings were neutral to litmus; washed with acetone and dried in the oven at ca. 120°C for 6-8 h. Dimethyl sulphate, b.p. 72-73°C (13 mm) and boron trifluoride etherate, b.p. 46°C (10 mm) were purified as recommended.³⁸ Titanium tetrachloride was obtained from Riedel-Dehäneg AG Seelze-Hannover. Anhydrous zinc bromide was obtained from Koch-Light Laboratories Ltd.

Chromatographic techniques as described in I.A.4 were used. Collection of physical data was done using the different instruments mentioned in I.A.4. The GC analyses were done on a Varian Gas Chromatograph.

I.B.4.1 Preparating of Starting Materials

The compound 4-methylanisole (23) was prepared by the reaction of p-cresol (22) and dimethyl sulphate in the presence of sodium hydroxide, b.p. 168-170°C (760 mm).²⁹

Preparation of Methoxyethoxymethyl chloride (28, MEM chloride)



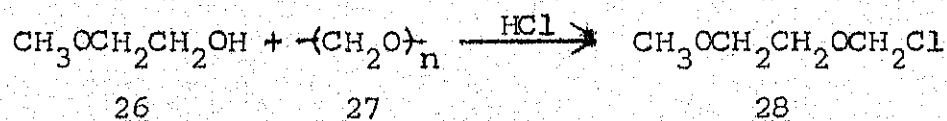
from sodium followed by magnesium ethoxide. Anhydrous liquid ammonia was obtained by distillation from sodium. Magnesium turnings were cleaned by washing with dilute hydrochloric acid, followed by distilled water, until the washings were neutral to litmus; washed with acetone and dried in the oven at ca. 120°C for 6-8 h. Dimethyl sulphate, b.p. 72-73°C (13 mm) and boron trifluoride etherate, b.p. 46°C (10 mm) were purified as recommended.³⁸ Titanium tetrachloride was obtained from Riedel-Dehāeneg AG Seelze-Hannover. Anhydrous zinc bromide was obtained from Koch-Light Laboratories Ltd.

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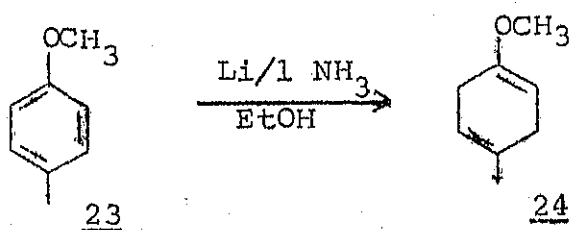
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Preparation of Methoxyethoxymethyl chloride (28, MEM chloride)



A mixture of methoxyethanol (26, 76 g, 1 mol) and para-formaldehyde (27, 30.3 g, 1 mol) was treated with dry hydrogen chloride gas in a steady stream, with stirring at 0°C, until the reaction mixture became clear. The resulting solution was diluted with pentane (300 mL) and dried over anhydrous magnesium sulphate (50 g) at 5°C for 3 h. The solution was filtered and pentane was evaporated to afford 94 g of MEM chloride 28 (76%), b.p. 50-52°C (13 mm).

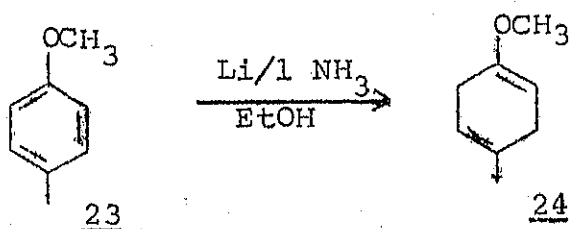
I.B.4.2 Preparation of 1-Methoxy-4-methyl-1,4-cyclohexadiene (24)



A solution of redistilled 4-methylanisole (23, 20 g, 164 mmol) in tetrahydrofuran (150 mL) and absolute ethanol (40 mL) was added to redistilled liquid ammonia (500 mL). Small pieces of lithium ribbon (5.7 g, 820 mmol) were added over a period of 0.25 h. Stirring was continued by means of a mechanical stirrer for 0.5 h, when the blue colour of the solution disappeared. Ammonium chloride solid was added until the excess lithium got destroyed. Ammonia was allowed to evaporate at room temperature. The curdy precipitate was dissolved in water and extracted with ether (4 x 100 mL). The ether extract was washed with brine until the washings were neutral to litmus and dried over anhydrous magnesium sulphate. The solvent was

A mixture of methoxyethanol (26, 76 g, 1 mol) and para-formaldehyde (27, 30.3 g, 1 mol) was treated with dry hydrogen chloride gas in a steady stream, with stirring at 0°C, until the reaction mixture became clear. The resulting solution was diluted with pentane (300 mL) and dried over anhydrous magnesium sulphate (50 g) at 5°C for 3 h. The solution was filtered and pentane was evaporated to afford 94 g of MEM chloride 28 (76%), b.p. 50-52°C (13 mm).

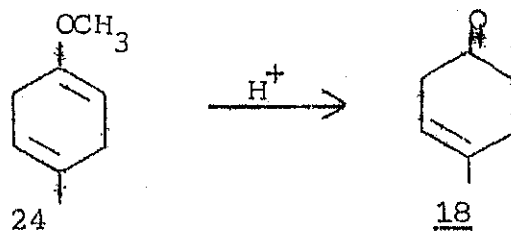
I.B.4.2 Preparation of 1-Methoxy-4-methyl-1,4-cyclohexadiene (24)



A solution of redistilled 4-methylanisole (23, 20 g, 164 mmol) in tetrahydrofuran (150 mL) and absolute ethanol (40 mL) was added to redistilled liquid ammonia (500 mL). Small pieces of lithium ribbon (5.7 g, 820 mmol) were added over a period of 0.25 h. Stirring was continued by means of a mechanical stirrer for 0.5 h, when the blue colour of the solution disappeared. Ammonium chloride solid was added until the excess lithium got destroyed. Ammonia was allowed to evaporate at room temperature. The curdy precipitate was dissolved in water and extracted with ether (4 x 100 mL). The ether extract was washed with brine until the washings were neutral to litmus and dried over anhydrous magnesium sulphate. The solvent was

evaporated under reduced pressure and distilled to afford 17 g of 24 (83%), b.p. 62-64° (15 mm), [lit.²⁸ b.p. 128-130°C (250 mm)].

I.B.4.3 Preparation of 4-Methyl-3-cyclohexenone (18)

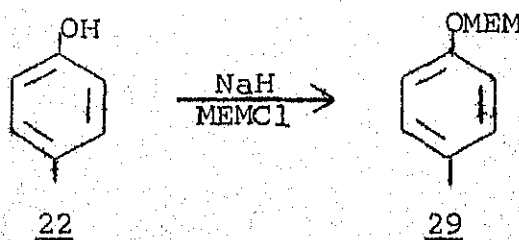


A solution of 24 (5.0 g, 40.3 mmol) in methanol (20 mL) was thoroughly shaken with 10% sulphuric acid (200 mL) for ten minutes. The mixture was extracted with ether (2 x 100 mL). The ether extract was washed with brine (2 x 100 mL) and dried over anhydrous potassium carbonate. Evaporation of ether followed by distillation afforded 3.6 g (81%) of 18, b.p. 68-69°C (18 mm), [lit.²⁸ b.p. 37-37.5°C (2.5 mm)].

IR (thin film): 1720 ($\nu_{C=O}$).

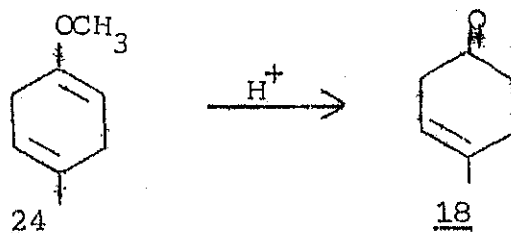
PMR (CCl_4): 1.79 (m, 3H, $-CH_3$); 2.42 (m, 4H, $-CH_2-$); 2.75 (m, 2H, $-CH_2-$); 5.46 (m, 1H, vinylic).

I.B.4.4 Preparation of 4-Methoxyethoxymethoxytoluene (29)



evaporated under reduced pressure and distilled to afford 17 g of 24 (83%), b.p. 62-64° (15 mm), [lit.²⁸ b.p. 128-130°C (250 mm)].

I.B.4.3 Preparation of 4-Methyl-3-cyclohexenone (18)

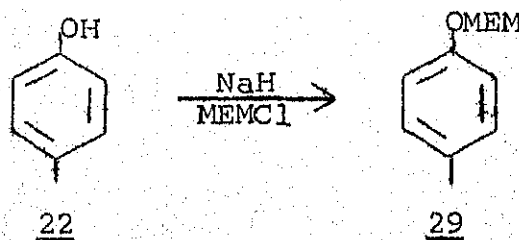


A solution of 24 (5.0 g, 40.3 mmol) in methanol (20 mL) was thoroughly shaken with 10% sulphuric acid (200 mL) for ten minutes. The mixture was extracted with ether (2 x 100 mL). The ether extract was washed with brine (2 x 100 mL) and dried over anhydrous potassium carbonate. Evaporation of ether followed by distillation afforded 3.6 g (81%) of 18, b.p. 68-69°C (18 mm), [lit.²⁸ b.p. 37-37.5°C (2.5 mm)].

IR (thin film): 1720 ($\nu_{C=O}$).

PMR (CCl_4): 1.79 (m, 3H, $-CH_3$); 2.42 (m, 4H, $-CH_2-$); 2.75 (m, 2H, $-CH_2-$); 5.46 (m, 1H, vinylic).

I.B.4.4 Preparation of 4-Methoxyethoxymethoxytoluene (29)

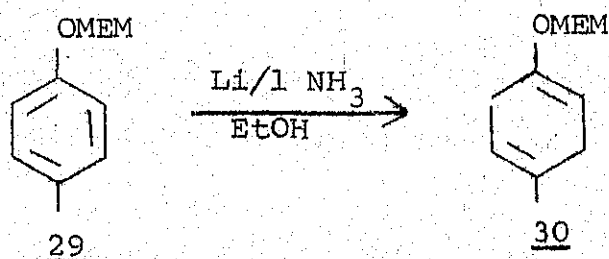


To a suspension of sodium hydride (11.3 g of a 50% oil dispersion, washed thrice with dry petroleum ether, 236 mmol) in anhydrous tetrahydrofuran (20 mL), was added dropwise over 1 h, a solution of p-cresol (12.7 g, 118 mmol) in tetrahydrofuran (60 mL) at ca. 0°C. The reaction mixture was stirred at 0°C until the hydrogen evolution ceased and then for an additional 0.25 h at room temperature (30°C). To the resulting mixture at 0°C, MEM chloride (22 g, 177 mmol) was added dropwise over 1 h. The reaction mixture was warmed to room temperature and stirred for 36 h. Excess sodium hydride was destroyed by careful addition of water and the reaction mixture was extracted with ether (3 x 100 mL). The combined extract was washed with 20% aqueous sodium hydroxide solution (2 x 50 mL), followed by brine. The ether extract was dried over anhydrous magnesium sulphate, filtered and concentrated. Distillation of the crude product gave 17.9 g (78%) of the MEM ether 29, b.p. 128-132°C (11 mm).

IR (thin film): 1220, 1100, 1000 ($\nu_{\text{C-O-C}}$).

PMR (CCl_4): 2.33 (s, 3H, $-\text{CH}_3$); 3.36 (s, 3H, $-\text{CH}_3$); 3.62 (m, 4H, $-\text{CH}_2$); 5.23 (s, 2H, $-\text{CH}_2$); 6.89 (m, 4H, aromatic).

I.B.4.5 Preparation of 1-Methoxyethoxymethoxy-4-methyl-1,4-cyclohexadiene (30)

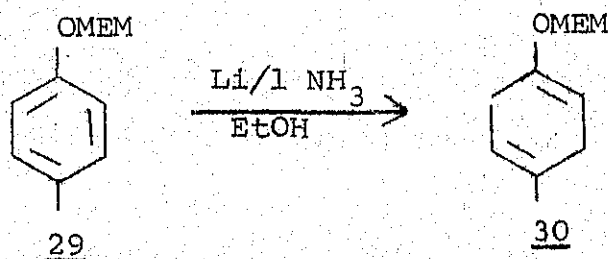


To a suspension of sodium hydride (11.3 g of a 50% oil dispersion, washed thrice with dry petroleum ether, 236 mmol) in anhydrous tetrahydrofuran (20 mL), was added dropwise over 1 h, a solution of p-cresol (12.7 g, 118 mmol) in tetrahydrofuran (60 mL) at ca. 0°C. The reaction mixture was stirred at 0°C until the hydrogen evolution ceased and then for an additional 0.25 h at room temperature (30°C). To the resulting mixture at 0°C, MEM chloride (22 g, 177 mmol) was added dropwise over 1 h. The reaction mixture was warmed to room temperature and stirred for 36 h. Excess sodium hydride was destroyed by careful addition of water and the reaction mixture was extracted with ether (3 x 100 mL). The combined extract was washed with 20% aqueous sodium hydroxide solution (2 x 50 mL), followed by brine. The ether extract was dried over anhydrous magnesium sulphate, filtered and concentrated. Distillation of the crude product gave 17.9 g (78%) of the MEM ether 29, b.p. 128-132°C (11 mm).

IR (thin film): 1220, 1100, 1000 ($\nu_{\text{C-O-C}}$).

PMR (CCl_4): 2.33 (s, 3H, $-\text{CH}_3$); 3.36 (s, 3H, $-\text{CH}_3$); 3.62 (m, 4H, $-\text{CH}_2$); 5.23 (s, 2H, $-\text{CH}_2$); 6.89 (m, 4H, aromatic).

I.B.4.5 Preparation of 1-Methoxyethoxymethoxy-4-methyl-1,4-cyclohexadiene (30)

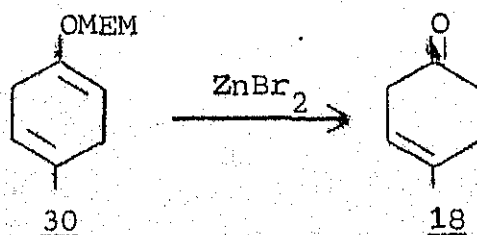


Lithium metal (2.4 g, 345.8 mmol) was added rapidly with efficient mechanical stirring to redistilled liquid ammonia (400 mL). After stirring for 0.25 h, a solution of 29 (10.2 g, 52 mmol) in dry tetrahydrofuran (40 mL) and absolute ethanol (10 mL) was added dropwise over 0.3 h. The reaction mixture was refluxed for 3 h. The excess lithium was carefully destroyed by the addition of solid ammonium chloride. The ammonia was allowed to evaporate. The curdy paste was taken in water and extracted with ether (5 x 100 mL). The ether extract was washed with brine (100 mL) and dried over anhydrous magnesium sulphate. The solution was filtered and evaporated to afford a liquid which was distilled to give 9.28 g (91%) of 30, b.p. 130-135°C (12 mm)

IR (thin film): 1665, 1610 ($\nu_{\text{C}=\text{C}-\text{O}}$), 1100, 1060 ($\nu_{\text{C}-\text{O}-\text{C}}$).

PMR (CCl_4): 1.66 (s, 3H, $-\text{CH}_3$); 2.66 (br, s, 4H, $-\text{CH}_2$); 3.33 (s, 3H, $-\text{CH}_3$); 3.53 (m, 4H, $-\text{CH}_2$); 4.84 (s, 1H, vinylic); 5.0 (s, 2H, $-\text{CH}_2$); 5.33 (m, 1H, vinylic).

I.B.4.6 Deprotection of the Dihydro MEM Ether 30 with Anhydrous Zinc Bromide



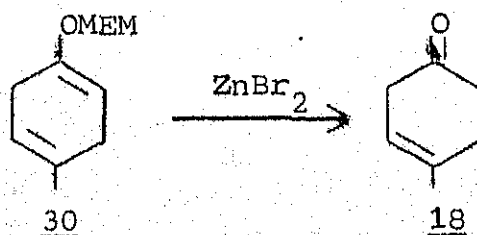
To a solution of 1-methoxyethoxymethoxy-4-methyl-1,4-cyclohexadiene (30, 8.9 g, 45 mmol) in dichloromethane (300 mL)

Lithium metal (2.4 g, 345.8 mmol) was added rapidly with efficient mechanical stirring to redistilled liquid ammonia (400 mL). After stirring for 0.25 h, a solution of 29 (10.2 g, 52 mmol) in dry tetrahydrofuran (40 mL) and absolute ethanol (10 mL) was added dropwise over 0.3 h. The reaction mixture was refluxed for 3 h. The excess lithium was carefully destroyed by the addition of solid ammonium chloride. The ammonia was allowed to evaporate. The curdy paste was taken in water and extracted with ether (5 x 100 mL). The ether extract was washed with brine (100 mL) and dried over anhydrous magnesium sulphate. The solution was filtered and evaporated to afford a liquid which was distilled to give 9.28 g (91%) of 30, b.p. 130-135°C (12 mm)

IR (thin film): 1665, 1610 ($\nu_{\text{C}=\text{C}-\text{O}}$), 1100, 1060 ($\nu_{\text{C}-\text{O}-\text{C}}$).

PMR (CCl_4): 1.66 (s, 3H, $-\text{CH}_3$); 2.66 (br, s, 4H, $-\text{CH}_2$); 3.33 (s, 3H, $-\text{CH}_3$); 3.53 (m, 4H, $-\text{CH}_2$); 4.84 (s, 1H, vinylic); 5.0 (s, 2H, $-\text{CH}_2$); 5.33 (m, 1H, vinylic).

I.B.4.6 Deprotection of the Dihydro MEM Ether 30 with Anhydrous Zinc Bromide

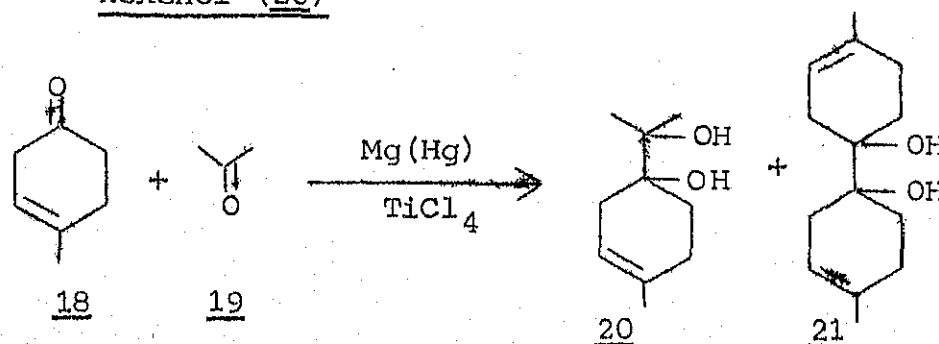


To a solution of 1-methoxyethoxymethoxy-4-methyl-1,4-cyclohexadiene (30, 8.9 g, 45 mmol) in dichloromethane (300 mL)

containing 1% nitromethane, was added anhydrous zinc bromide (20.25 g, 90 mmol) in portions with efficient mechanical stirring. The resulting mixture was stirred at room temperature for 3 h and then was washed successively with saturated sodium bicarbonate solution (50 mL) and brine (50 mL). The aqueous washings were extracted with ether (2 x 50 mL) and the combined organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated to afford 4.28 g (80%) of 18, b.p. 68-69°C (18 mm), [lit.²⁸ b.p. 37-37.5°C (2.5 mm)].

IR (thin film): 1720 ($\nu_{\text{C=O}}$).

I.B.4.7 Preparation of 1-(2'-hydroxypropyl)-4-methyl-3-cyclohexenol (20)

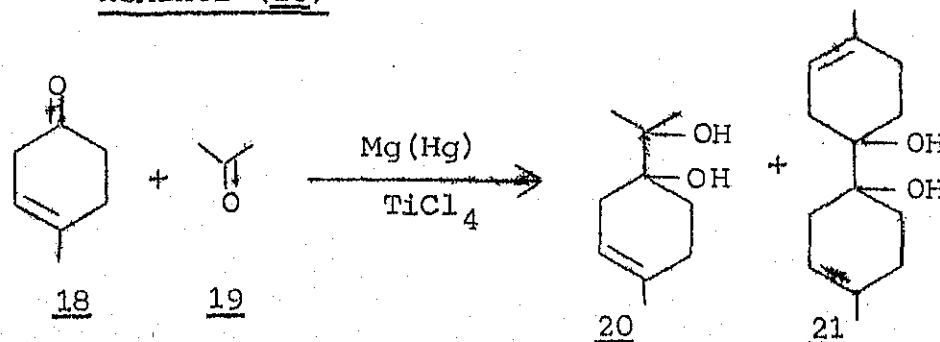


To a solution of mercuric chloride (1.85 g, 6.83 mmol) in anhydrous tetrahydrofuran (30 mL), were added freshly cleaned magnesium turnings (6.01 g, 247.3 mmol) and the resulting mixture was stirred at room temperature under nitrogen atmosphere for 0.25 h. The turbid supernatant liquid was withdrawn by syringe and the amalgam was washed with three portions (15 mL) of tetrahydrofuran. The reaction mixture was cooled to -10°C

containing 1% nitromethane, was added anhydrous zinc bromide (20.25 g, 90 mmol) in portions with efficient mechanical stirring. The resulting mixture was stirred at room temperature for 3 h and then was washed successively with saturated sodium bicarbonate solution (50 mL) and brine (50 mL). The aqueous washings were extracted with ether (2 x 50 mL) and the combined organic extract was dried over anhydrous magnesium sulphate, filtered and concentrated to afford 4.28 g (80%) of 18, b.p. 68-69°C (18 mm), [lit.²⁸ b.p. 37-37.5°C (2.5 mm)].

IR (thin film): 1720 ($\nu_{\text{C=O}}$).

I.B.4.7 Preparation of 1-(2'-hydroxypropyl)-4-methyl-3-cyclohexenol (20)



To a solution of mercuric chloride (1.85 g, 6.83 mmol) in anhydrous tetrahydrofuran (30 mL), were added freshly cleaned magnesium turnings (6.01 g, 247.3 mmol) and the resulting mixture was stirred at room temperature under nitrogen atmosphere for 0.25 h. The turbid supernatant liquid was withdrawn by syringe and the amalgam was washed with three portions (15 mL) of tetrahydrofuran. The reaction mixture was cooled to -10°C

after adding tetrahydrofuran (90 mL). Titanium tetrachloride (23.49 g, 13.6 mL, 123.6 mmol) was added dropwise. The walls of the reaction flask were washed with THF (20 mL) and a solution of 4-methyl-3-cyclohexenone (18, 3.4 g, 30.9 mmol) and acetone (6.98 g, 120.4 mmol) in tetrahydrofuran (30 mL) was added. The purple reaction mixture was stirred for 0.75 h at -10°C and then treated with 10% aqueous potassium carbonate solution (10 mL) briefly for ten minutes. Ether (100 mL) was added and the mixture was filtered through a pad of celite and sand layers, packed alternatively. The filtrate was washed with saturated sodium chloride solution (50 mL) and dried over anhydrous magnesium sulphate. The ether extract was filtered and concentrated to afford a viscous oil. The crude product was purified by flash column chromatography which yielded 0.342 g (5%) of 1,1'-dihydroxy-bis(4-methyl-3-cyclohexene) (21), m.p. $94-95^{\circ}\text{C}$ (elution with 3:7 ether-petroleum ether) and 2.99 g (57%) of the unsymmetrical pinacol 20 (elution with 3:7 ether-petroleum ether), and also acetone pinacol.

Symmetrical pinacol 21

IR (CHCl_3): 3430 ($\nu_{\text{O-H}}$).

PMR (CDCl_3): 1.66 (s, 6H, $-\text{CH}_3$); 1.2 - 2.6 (m, 14H, $-\text{CH}_2$, $-\text{OH}$); 5.27 (br, s, 2H, vinylic).

MS (m/e): 204 ($\text{M}^+ - 18$), 186, 154, 136, 121, 111, 95, 93, 86, 81, 79, 77, 68, 67, 55, 53.

after adding tetrahydrofuran (90 mL). Titanium tetrachloride (23.49 g, 13.6 mL, 123.6 mmol) was added dropwise. The walls of the reaction flask were washed with THF (20 mL) and a solution of 4-methyl-3-cyclohexenone (18, 3.4 g, 30.9 mmol) and acetone (6.98 g, 120.4 mmol) in tetrahydrofuran (30 mL) was added. The purple reaction mixture was stirred for 0.75 h at -10°C and then treated with 10% aqueous potassium carbonate solution (10 mL) briefly for ten minutes. Ether (100 mL) was added and the mixture was filtered through a pad of celite and sand layers, packed alternatively. The filtrate was washed with saturated sodium chloride solution (50 mL) and dried over anhydrous magnesium sulphate. The ether extract was filtered and concentrated to afford a viscous oil. The crude product was purified by flash column chromatography which yielded 0.342 g (5%) of 1,1'-dihydroxy-bis(4-methyl-3-cyclohexene) (21), m.p. $94-95^{\circ}\text{C}$ (elution with 3:7 ether-petroleum ether) and 2.99 g (57%) of the unsymmetrical pinacol 20 (elution with 3:7 ether-petroleum ether), and also acetone pinacol.

Symmetrical pinacol 21

IR (CHCl_3): 3430 ($\nu_{\text{O-H}}$).

PMR (CDCl_3): 1.66 (s, 6H, $-\text{CH}_3$); 1.2 - 2.6 (m, 14H, $-\text{CH}_2$, $-\text{OH}$); 5.27 (br, s, 2H, vinylic).

MS (m/e): 204 ($\text{M}^+ - 18$), 186, 154, 136, 121, 111, 95, 93, 86, 81, 79, 77, 68, 67, 55, 53.

Unsymmetrical pinacol 20

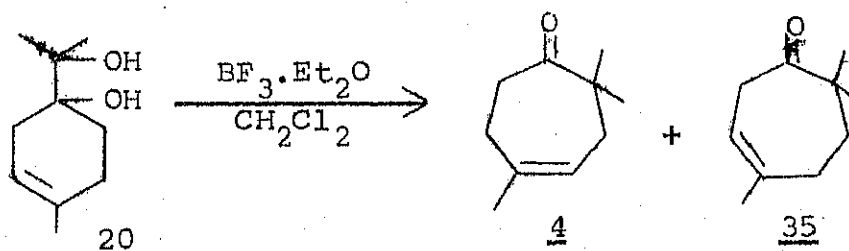
IR (CHCl_3): 3425 ($\nu_{\text{O-H}}$).

PMR (CDCl_3): 1.2 (s, 3H, $-\text{CH}_3$); 1.22 (s, 3H, $-\text{CH}_3$); 1.69 (s, 3H, $-\text{CH}_3$); 1.48 - 2.44 (m, 8H, $-\text{CH}_2$, $-\text{OH}$); 5.32 (br, s, 1H, vinylic).

MS (m/e): 152 ($\text{M}^+ - 18$), 137, 119, 111, 110, 94, 93, 91, 86, 84, 81, 79, 68, 59, 55, 43.

Anal. for $\text{C}_{10}\text{H}_{18}\text{O}_2$: Calcd. C, 78.94; H, 11.84.

Found C, 78.84; H, 11.91.

I.B.4.8 Ring Expansion of Diol 20

To a solution of unsymmetrical pinacol 20 (0.34 g, 2 mmol) in dichloromethane (4 mL), added boron trifluoride etherate (0.284 g, 2 mmol) at ca. 0°C. The reaction mixture was stirred for 12 h at 0°C under nitrogen atmosphere. Cold water (10 mL) was added and the reaction mixture was extracted with ether (3 x 20 mL). The combined organic extract was washed with cold saturated sodium bicarbonate solution (10 mL), followed by brine (10 mL). The ether extract was dried over anhydrous magnesium sulphate, filtered and concentrated to afford 0.24 g (82%) of a mixture of two products in the ratio 30:70 (GC-MS,

Unsymmetrical pinacol 20

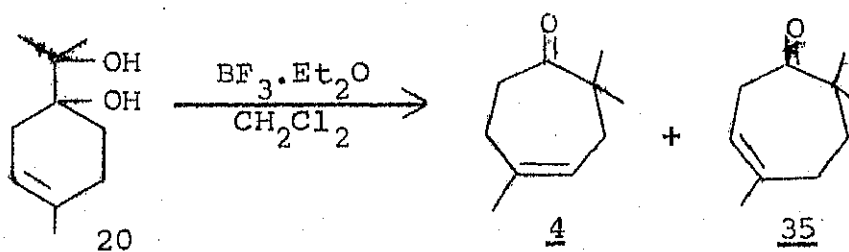
IR (CHCl_3): 3425 ($\nu_{\text{O-H}}$).

PMR (CDCl_3): 1.2 (s, 3H, $-\text{CH}_3$); 1.22 (s, 3H, $-\text{CH}_3$); 1.69 (s, 3H, $-\text{CH}_3$); 1.48 - 2.44 (m, 8H, $-\text{CH}_2$, $-\text{OH}$); 5.32 (br, s, 1H, vinylic).

MS (m/e): 152 ($\text{M}^+ - 18$), 137, 119, 111, 110, 94, 93, 91, 86, 84, 81, 79, 68, 59, 55, 43.

Anal. for $\text{C}_{10}\text{H}_{18}\text{O}_2$: Calcd. C, 78.94; H, 11.84.

Found C, 78.84; H, 11.91.

I.B.4.8 Ring Expansion of Diol 20

To a solution of unsymmetrical pinacol 20 (0.34 g, 2 mmol) in dichloromethane (4 mL), added boron trifluoride etherate (0.284 g, 2 mmol) at ca. 0°C. The reaction mixture was stirred for 12 h at 0°C under nitrogen atmosphere. Cold water (10 mL) was added and the reaction mixture was extracted with ether (3 x 20 mL). The combined organic extract was washed with cold saturated sodium bicarbonate solution (10 mL), followed by brine (10 mL). The ether extract was dried over anhydrous magnesium sulphate, filtered and concentrated to afford 0.24 g (82%) of a mixture of two products in the ratio 30:70 (GC-MS,

$M^+ = 152.1$). The crude product mixture was purified by preparative gas chromatography (10% SE-30, 140°C), to yield 0.072 g (24%) of 2,2,5-trimethyl-4-cycloheptenone (35) and 0.16 g (56.6%) of 2,2,5-trimethyl-3-cycloheptenone (4).

Compound 35

IR (thin film): 1710 ($\nu_{C=O}$).

PMR ($CDCl_3$): 1.12 (s, 6H, $-CH_3$); 1.66 (s, 3H, $-CH_3$); 1.78 - 2.4 (m, 4H, $-\overset{|}{CH}_2$); 3.18 (d, 2H, $-\overset{|}{CH}_2$); 5.32 (m, 1H, vinylic).

MS (m/e): 152.1 (M^+), 124, 109, 95, 81, 68, 67, 56, 53.

Karahanaenone (4)

IR (thin film): 1710 ($\nu_{C=O}$).

PMR ($CDCl_3$): 1.08 (s, 6H, $-CH_3$); 1.67 (s, 3H, $-CH_3$); 2.25 (m, 4H, $-\overset{|}{CH}_2$); 2.74 (t, 2H, $-\overset{|}{CH}_2$, $J = 7$ Hz); 5.5 (br, 1H, vinylic).

MS (m/e): 152.1 (M^+), 137, 109, 97, 95, 81, 79, 70, 69, 67, 55, 53, 43, 41.

I.B.4.9 Preparation of Semicarbazone of 4

To a solution of 0.016 g (0.15 mmol) of semicarbazide hydrochloride and sodium acetate (0.02 g, 0.24 mmol) in water (1 mL) was added compound 4 (0.015 g, 0.1 mmol) in ethanol

$M^+ = 152.1$). The crude product mixture was purified by preparative gas chromatography (10% SE-30, 140°C), to yield 0.072 g (24%) of 2,2,5-trimethyl-4-cycloheptenone (35) and 0.16 g (56.6%) of 2,2,5-trimethyl-3-cycloheptenone (4).

Compound 35

IR (thin film): 1710 ($\nu_{C=O}$).

PMR ($CDCl_3$): 1.12 (s, 6H, $-CH_3$); 1.66 (s, 3H, $-CH_3$); 1.78 - 2.4 (m, 4H, $-\overset{|}{CH}_2$); 3.18 (d, 2H, $-\overset{|}{CH}_2$); 5.32 (m, 1H, vinylic).

MS (m/e): 152.1 (M^+), 124, 109, 95, 81, 68, 67, 56, 53.

Karahanaenone (4)

IR (thin film): 1710 ($\nu_{C=O}$).

PMR ($CDCl_3$): 1.08 (s, 6H, $-CH_3$); 1.67 (s, 3H, $-CH_3$); 2.25 (m, 4H, $-\overset{|}{CH}_2$); 2.74 (t, 2H, $-\overset{|}{CH}_2$, $J = 7$ Hz); 5.5 (br, 1H, vinylic).

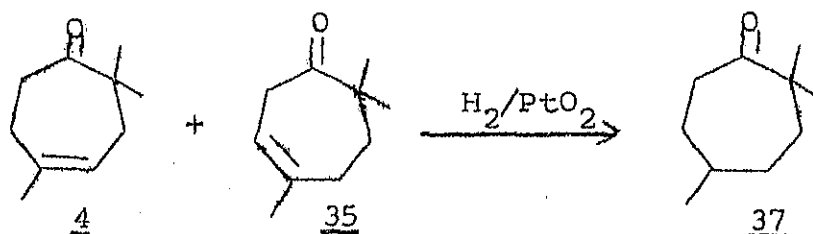
MS (m/e): 152.1 (M^+), 137, 109, 97, 95, 81, 79, 70, 69, 67, 55, 53, 43, 41.

I.B.4.9 Preparation of Semicarbazone of 4

To a solution of 0.016 g (0.15 mmol) of semicarbazide hydrochloride and sodium acetate (0.02 g, 0.24 mmol) in water (1 mL) was added compound 4 (0.015 g, 0.1 mmol) in ethanol

(1 mL) and heated on the water bath at 70° for 0.24 hr. On cooling, colourless crystals of semicarbazone which separated out were collected by filtration (0.019 g, 95%). The semicarbazone was recrystallized from ethanol, m.p. 164-68°C (lit.¹⁶ m.p. 166-168°C).

I.B.4.10 Hydrogenation of the Crude Reaction Product of Ring Expansion Reaction



A solution of the mixture of isomers from the rearrangement reaction (0.03 g) and platinum oxide (0.005 g) in ethyl acetate (2 mL) was stirred under an atmosphere of hydrogen for 2 h. The catalyst was filtered off and the solvent was evaporated to afford 0.028 g of a liquid. The GC-analysis (10%, SE-30, 140°C) indicated the presence of only one compound (98% pure).

Dihydrokarahanaenone (37)

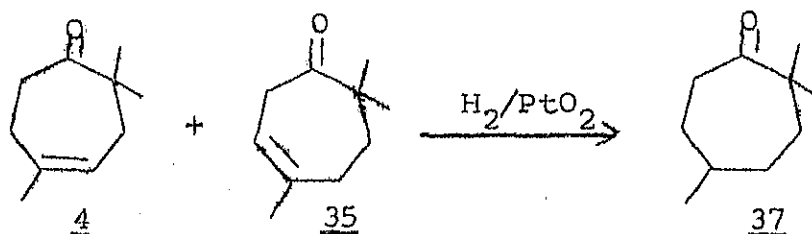
IR (thin film): 1700 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 0.95 (d, 3H, $-\text{CH}_3$, $J = 6$ Hz); 1.06 (s, 6H, $-\text{CH}_3$); 1.64 (m, 6H, $-\text{CH}_2$); 2.74 (m, 2H, $-\text{CH}_2$); 2.28 (m, 1H, $-\text{CH}$).

MS (m/s): 154.1 (M^+), 139, 121, 111, 110, 97, 95, 85, 83, 69, 55, 41.

(1 mL) and heated on the water bath at 70° for 0.24 hr. On cooling, colourless crystals of semicarbazone which separated out were collected by filtration (0.019 g, 95%). The semicarbazone was recrystallized from ethanol, m.p. 164-68°C (lit.¹⁶ m.p. 166-168°C).

I.B.4.10 Hydrogenation of the Crude Reaction Product of Ring Expansion Reaction



A solution of the mixture of isomers from the rearrangement reaction (0.03 g) and platinum oxide (0.005 g) in ethyl acetate (2 mL) was stirred under an atmosphere of hydrogen for 2 h. The catalyst was filtered off and the solvent was evaporated to afford 0.028 g of a liquid. The GC-analysis (10%, SE-30, 140°C) indicated the presence of only one compound (98% pure).

Dihydrokarahanaenone (37)

IR (thin film): 1700 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 0.95 (d, 3H, $-\text{CH}_3$, $J = 6$ Hz); 1.06 (s, 6H, $-\text{CH}_3$); 1.64 (m, 6H, $-\text{CH}_2$); 2.74 (m, 2H, $-\text{CH}_2$); 2.28 (m, 1H, $-\text{CH}$).

MS (m/s): 154.1 (M^+), 139, 121, 111, 110, 97, 95, 85, 83, 69, 55, 41.

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CHAPTER II

(PART A)

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF THE SEX PHEROMONE OF CIGARETTE BEETLE (SERRICORNIN)

II.A.1 ABSTRACT

The insect sex pheromone of cigarette beetle (Lasioderma serricorne F.), a cosmopolitan pest of cured tobacco leaves, has been the target molecule for the synthesis which has been achieved in twelve simple steps starting from readily available materials. The inherent symmetry possessed by the pheromone, 4,6-dimethyl-7-hydroxy-3-nonanone, has been made use of, in devising the synthetic strategy. In the course of the synthetic efforts, methodology has been developed for the cis-hydroxylation of olefins under anhydrous conditions using a stable and inexpensive reagent, cetyltrimethylammonium permanganate.

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II.A.2 INTRODUCTION

Chemical insecticides have become the predominant method of insect control, but their future is threatened by several intractable problems. The development of insect resistance to the generation of insecticides is recognised as a growing problem. Environmental damage to wildlife, eradication of beneficial insects and contamination of food by pesticide use are causing increasing concern.

As present insecticides become less effective, the development of new insecticidal compounds is becoming increasingly expensive. The search for broad spectrum insect toxicity could gradually be abandoned and a more selective 'biorational approach' be adopted. This strategy will encompass a thorough study of the physiology and biochemistry of the 'target' insect species. The aim will be to disrupt insect moulting, mating, egg-laying etc. Pesticide agents developed in this way will not be subject to the major inherent limitation of conventional chemical insecticides; they will be directed against a specific species of insects, leaving the remaining ecosystem of predatory insects, birds, wildlife and crop plants, undamaged.

One of the most promising and revolutionary type of these new insect control agents is the class of pheromones. Synthetic pheromones do not kill insects, but are capable of disrupting their normal behaviour. Their composition duplicates that of natural messenger compounds controlling insect mating, foraging,

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aggregation or response to danger. Pheromones (from Greek, pherin - to carry and horman - to excite) are classified according to the response they elicit. Sex pheromones are secreted by one sex to attract the other as an initial part of the mating process. They can be produced by either sex, though those produced by the female tend to be more effective over long distances. The compounds which comprise insect pheromones vary widely in type and structure but all pheromones are found to have some common characteristics. They all are mixtures of compounds. Of critical importance are the relative amounts of various compounds in a pheromone mixture. Each component must be present in the correct ratio if the pheromone is to be effective in attracting insects or modifying their behaviour.

No less than seven compounds have been isolated as components of the sex pheromone of the female tobacco budworm (Heliothis virescens). Two of the compounds by themselves arouse the male budworm but the seven-compound mixture attracts five times more males in field tests.

Since pheromones are carried by air currents, they must contain volatile compounds. This requirement imposes an upper limit on the size of the molecules encountered in pheromone mixtures. Most of them have less than twenty carbon atoms and these are often arranged in straight chain structures. Even with such relatively simple molecules, a large number of chemical isomers are possible and it is surprising that most insect

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species are able to distinguish enantiomers in pheromone mixtures.

The enantiomeric composition of a pheromone component might or might not be critically important in determining the response of the insect. In some species, the presence of one enantiomer inhibits the effect of the other. This is the case for the Japanese beetle 'Popillia japonica' which responds to a pheromone mixture only when it contains atleast 95% of the active enantiomer.

The ability of an insect to respond very selectively to one enantiomer does not necessarily preclude the use of an optically inactive mixture in synthetic pheromones. In the species 'Trogoderma granarium' the male responds actively to (-) 14-methyl-8-hexadecanal, but the presence of the (+) enantiomer does not interfere with the insect's response. The ambrosia beetle 'Trypodendron leniatum' responds equally well to both the enantiomers. Such insect species are more vulnerable to disruption of their pheromone communication since the manufacture of a synthetic pheromone would bypass the very substantial complexity introduced when optically active compounds are prepared and isolated.

Pheromones are usually produced in extremely small amounts (female insects generally produce 1-20 ng of sex pheromone). Separating and identifying the minute amounts of compounds in pheromone mixtures pose a difficult challenge for the laboratory

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worker. Pheromone samples are extracted from insect glands or absorbed from the airstream supplied to a group of insects. The components are generally separated by gas chromatography and the structure of each component is determined by spectroscopic techniques like high resolution infrared, proton magnetic resonance and mass spectrometry.

The high activity of pheromones at extremely low concentrations is an advantage when pheromones are manufactured and deployed. The action of a pheromone is highly specific. Amounts that can disrupt mating or other behaviour of one harmful insect species have virtually no effect on other insects, birds or animals. Thus, the pheromone can act in unison with natural predators of the insect pest in halting an infestation rather than destroying them.

Although most of the pheromones possess simple structures, the presence of π systems and chiral centres in their structural framework, together with their stereospecificity has rendered many syntheses non-trivial and has posed a considerable challenge in designing the synthetic strategy.^{1,2}

The cigarette beetle (Lasioderma serricorne F.) is a serious cosmopolitan pest of cured tobacco leaves. In the course of chemical studies for the pest management of the cigarette beetles, a sex pheromone produced by the beetles was isolated.³ In 1979, Chuman and coworkers reported the isolation and structural elucidation of this novel sex pheromone and

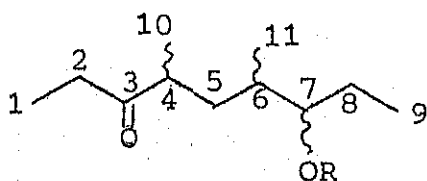
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identified it as 4,6-dimethyl-7-hydroxy-3-nonanone (1) based on the IR, PMR and CMR data.³ The pheromone was isolated in a minute quantity from the body of 65,000 female cigarette beetles and the preparative gas chromatographic purification was effected on the acetate of the sex pheromone 2 (ca. 1.5 mg) as the pheromone itself was found unstable towards heat. The structure of the pheromone was confirmed by Chuman et al. by carrying out two non-stereospecific syntheses to obtain the pheromone, named as Serricornin, as a diastereomeric mixture.^{4,5} However, the absolute stereochemistry at the three chiral centres remained unknown.

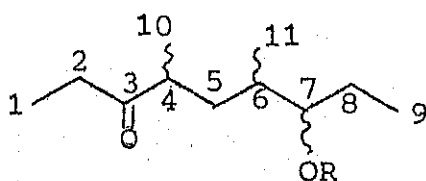


1, R = H

2, R = OCOCH₃

In 1981, Mori and coworkers synthesized (4RS, 6R, 7R)-1 and (4RS, 6R, 7S)-1 and established the (6S, 7S) stereochemistry of the natural product.⁶ As the chiral starting material, (2S, 3S)-threo- β -methylmalic acid (3) and diethyl (2R, 3S)-erythro- β -methylmalate (10) were employed and two diastereomers were independently synthesized in seventeen steps. The unknown configuration at C-4 was determined by the synthesis of (4S, 6R, 7R)-1, starting from glucose (11) in about nineteen steps and the absolute stereochemistry of Serricornin was assigned to be (4S, 6S, 7S)-1 (Scheme II.A.1 and II.A.2).⁷

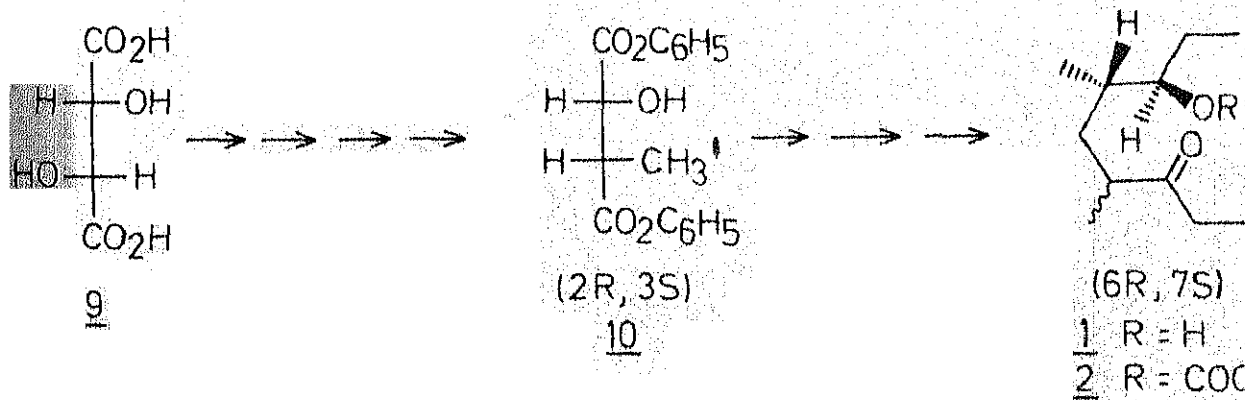
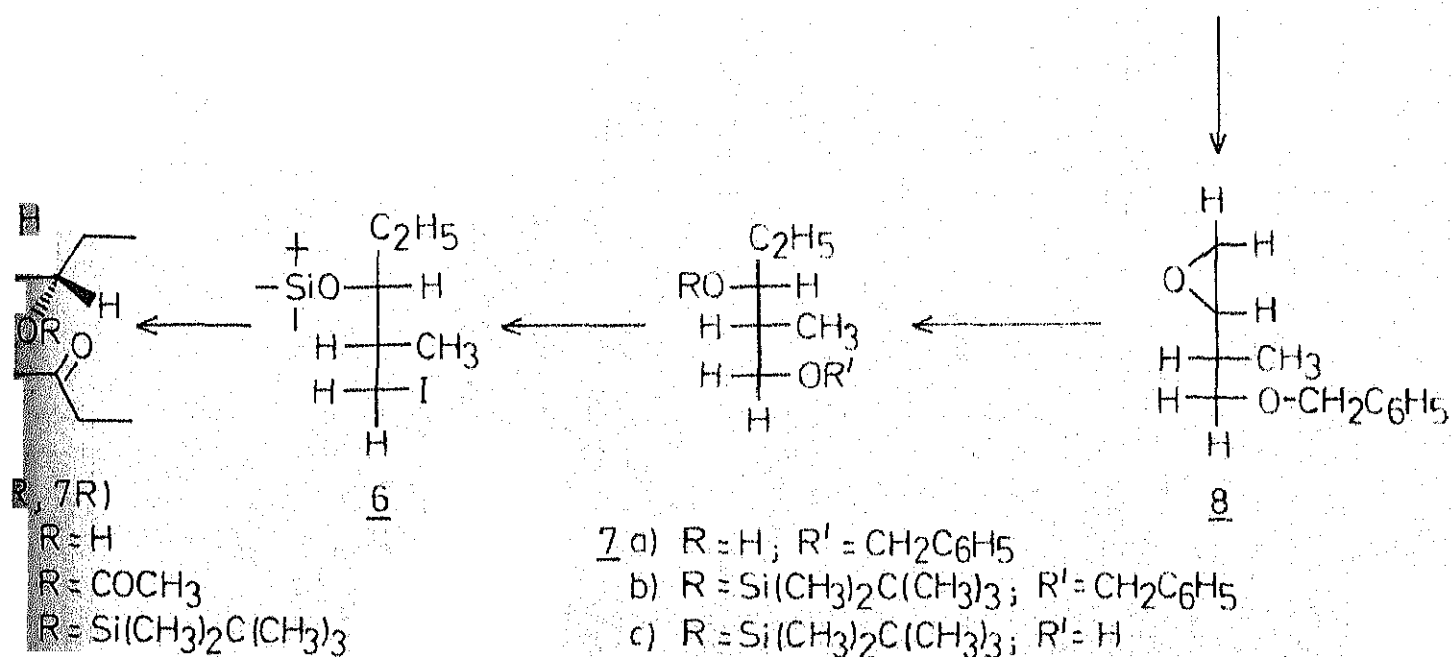
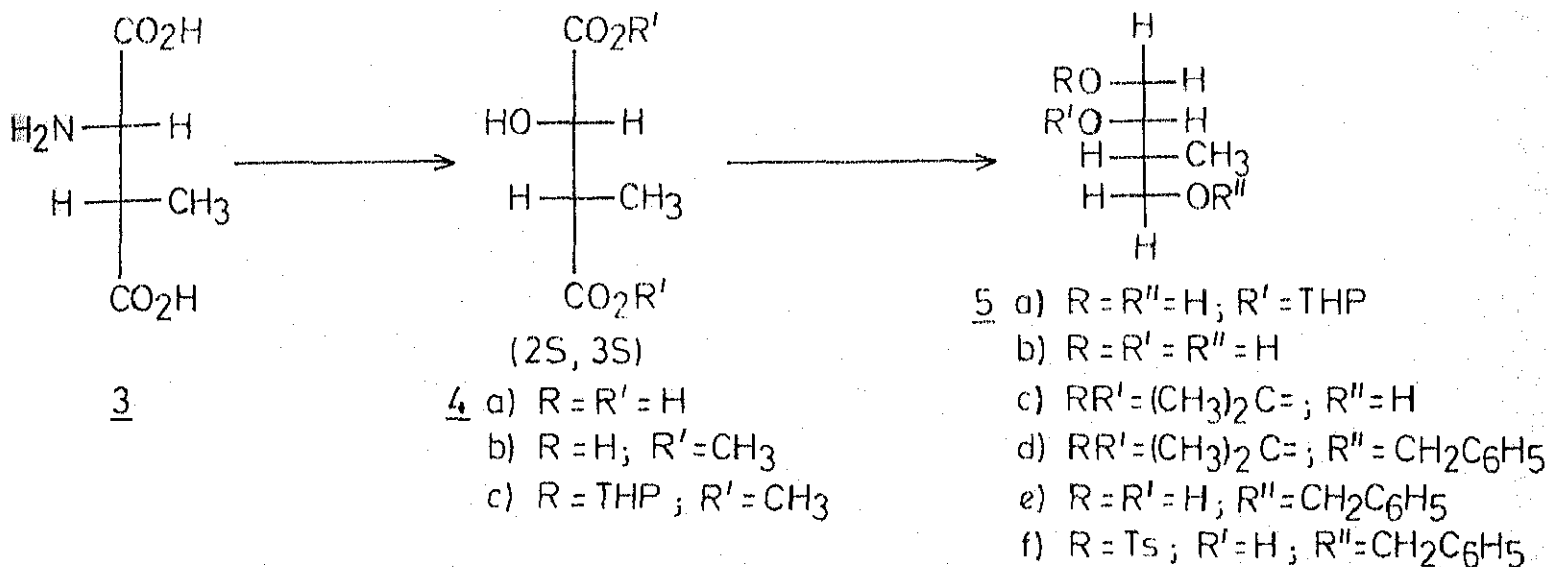
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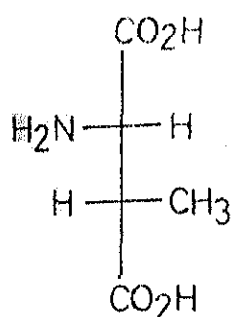
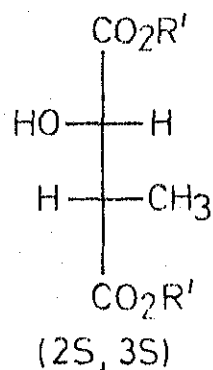


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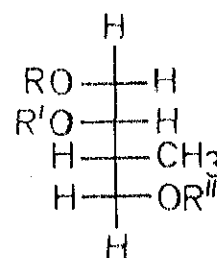
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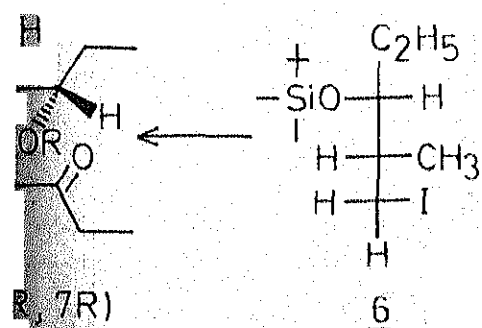


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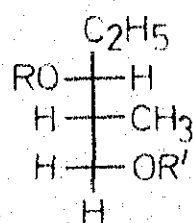
- 4 a) $\text{R} = \text{R}' = \text{H}$
 b) $\text{R} = \text{H}; \text{R}' = \text{CH}_3$
 c) $\text{R} = \text{THP}; \text{R}' = \text{CH}_3$



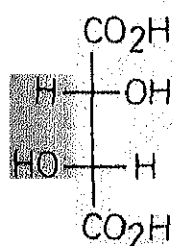
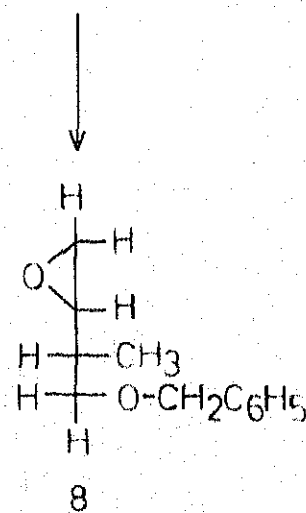
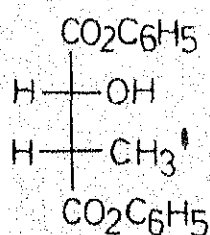
- 5 a) $\text{R} = \text{R}'' = \text{H}; \text{R}' = \text{THP}$
 b) $\text{R} = \text{R}' = \text{R}'' = \text{H}$
 c) $\text{RR}' = (\text{CH}_3)_2\text{C} =; \text{R}'' = \text{H}$
 d) $\text{RR}' = (\text{CH}_3)_2\text{C} =; \text{R}'' = \text{CH}_2\text{C}_6\text{H}_5$
 e) $\text{R} = \text{R}' = \text{H}; \text{R}'' = \text{CH}_2\text{C}_6\text{H}_5$
 f) $\text{R} = \text{Ts}; \text{R}' = \text{H}; \text{R}'' = \text{CH}_2\text{C}_6\text{H}_5$



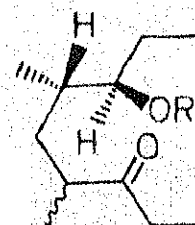
- 6 a) $\text{R} = \text{H}$
 b) $\text{R} = \text{COCH}_3$
 c) $\text{R} = \text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$



- 7 a) $\text{R} = \text{H}; \text{R}' = \text{CH}_2\text{C}_6\text{H}_5$
 b) $\text{R} = \text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3; \text{R}' = \text{CH}_2\text{C}_6\text{H}_5$
 c) $\text{R} = \text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3; \text{R}' = \text{H}$
 d) $\text{R} = \text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3; \text{R}' = \text{Ts}$

9

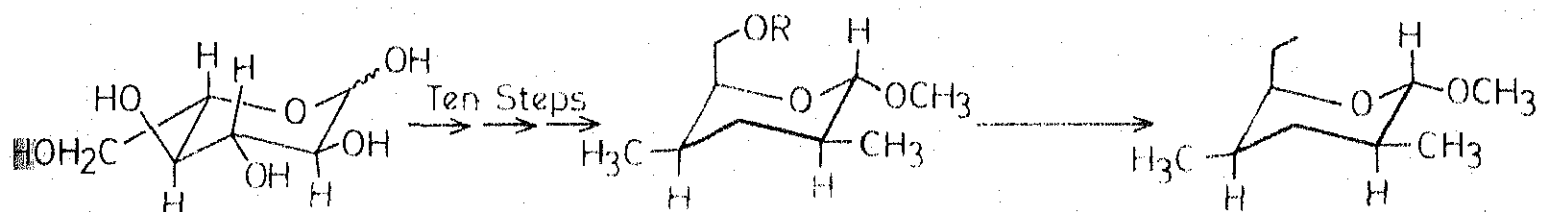
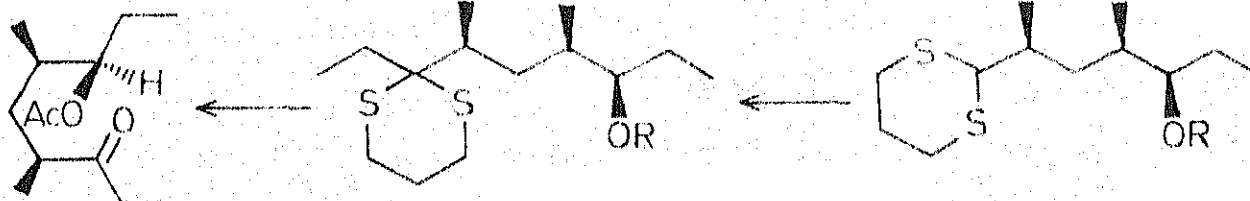
(2R, 3S)

10

(6R, 7S)

- 1 $\text{R} = \text{H}$
2 $\text{R} = \text{COCH}_3$

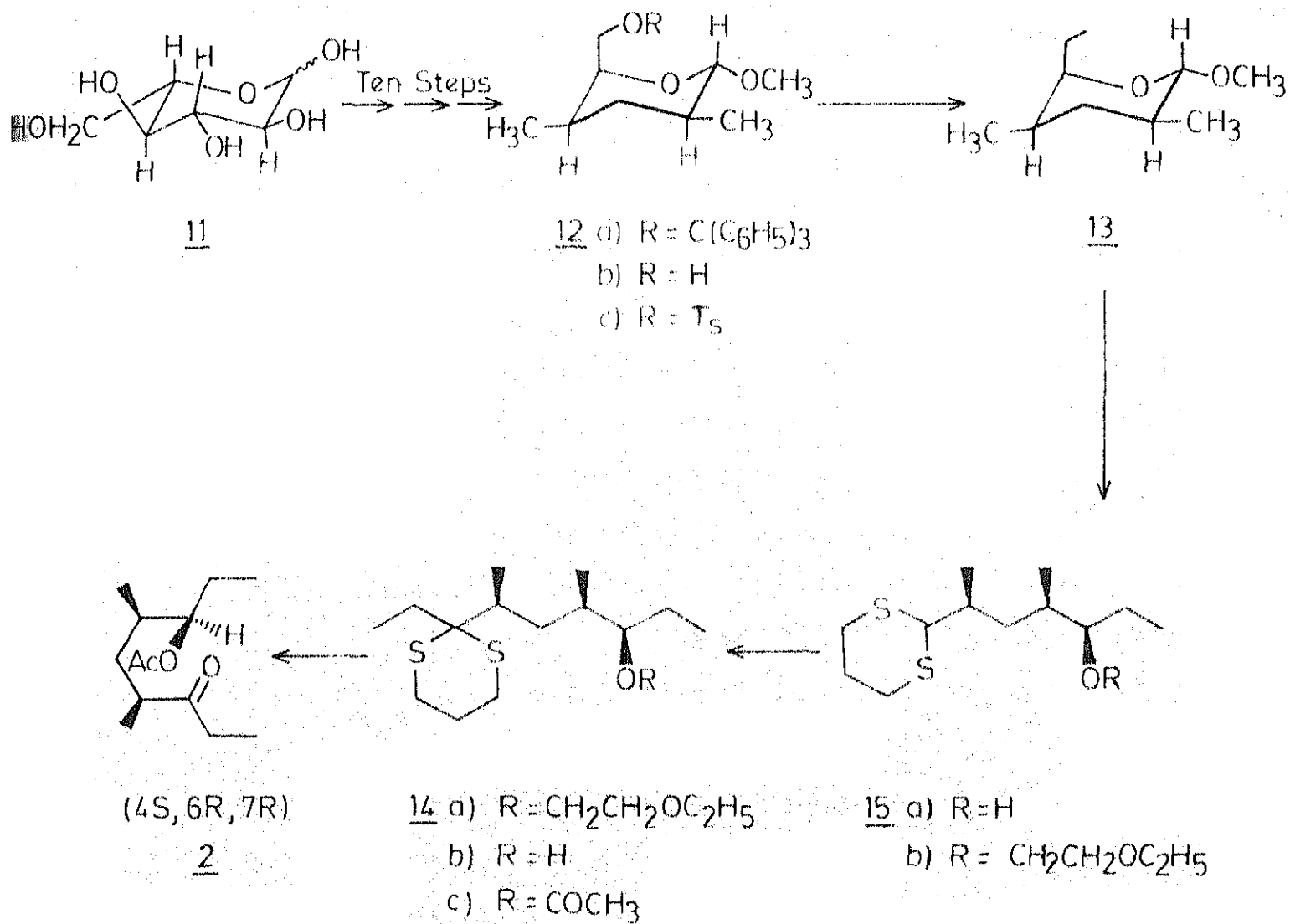
Scheme II-A-2

**11****12** a) $R = C(C_6H_5)_3$ b) $R = H$ c) $R = Ts$ **13**

(4S, 6R, 7R)

2**14** a) $R = CH_2CH_2OC_2H_5$ b) $R = H$ c) $R = COCH_3$ **15** a) $R = H$ b) $R = CH_2CH_2OC_2H_5$

Scheme II-A-2



The synthesis of the actual pheromone with its absolute stereochemistry is yet to be achieved. The symmetric molecular framework of Serricornin attracted our attention when it was first reported. With a view to synthesizing one or more of the isomers, we took up this project when the absolute configurations at the three asymmetric centres were not known.

II.A.3 RESULTS AND DISCUSSION

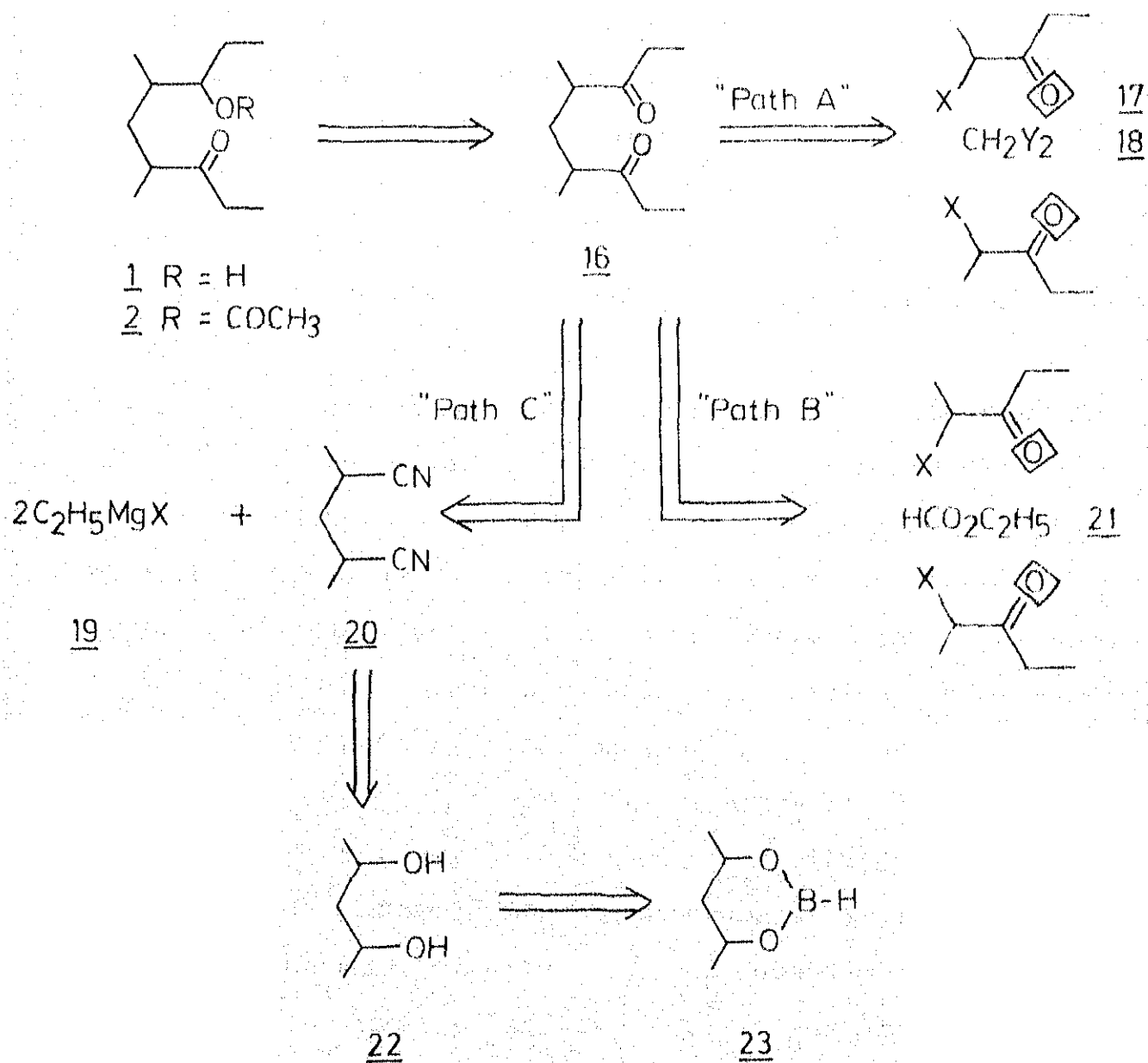
The inherent symmetry possessed by the pheromone structure offers attractive possibilities for the retrosynthetic analysis. Different synthetic strategies which have emerged from a straightforward retrosynthetic analysis are outlined in Scheme II.A.3. In the absence of any knowledge about the absolute configuration at the three chiral centres, initial attempts were focussed on a nonstereospecific synthesis of the pheromone 1. 'Path A' would lead by antithetic analysis to a reaction involving two molecules of 3-pentanone suitably substituted at the α -position, allowing for coupling via a methylene equivalent. 'Path B' would suggest a Grignard reaction with the α -bromo derivative of a suitably protected 3-pentanone and ethyl formate. The advantage of 'path C' would be that the meso and dl forms of the intermediates could be separated at an appropriate stage so that one or more of the stereoisomers can be synthesized.

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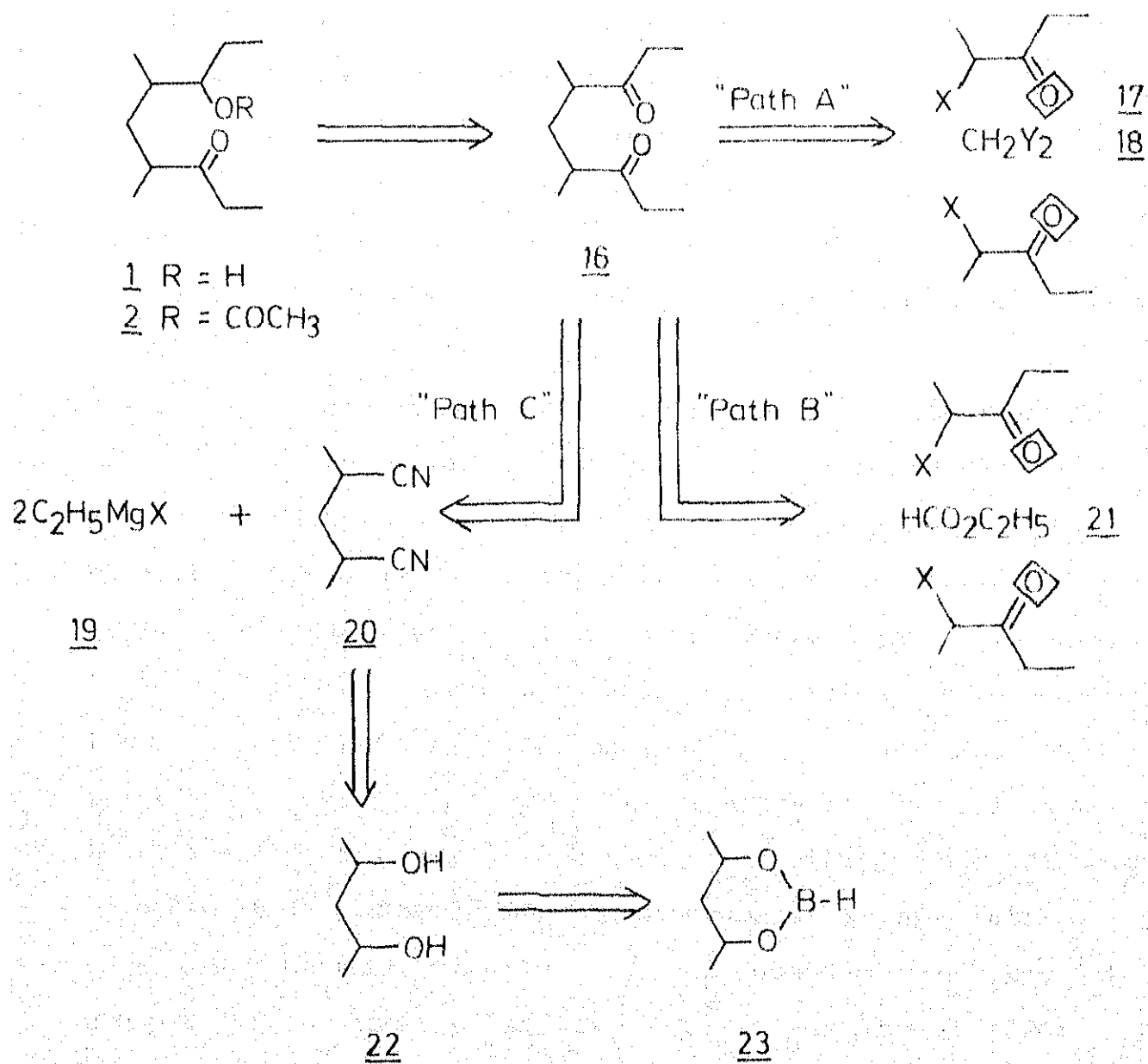
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Scheme II-A.3



Scheme II-A.3



The first approach that was studied was the dialkylation of malonic ester with the bromoacetal 17 ($X = Br$). Three different methods were looked at to synthesize 17. Bromination of 3-pentanone followed by acetalization with ethylene glycol in the presence of *p*-toluenesulphonic acid gave a very poor yield of the desired bromoacetal. An alternative method consisting of acetalization of 3-pentanone with ethylene glycol, followed by bromination using phenyltrimethylammonium tribromide (PTT)^{8,9} in tetrahydrofuran also gave inferior yields. Attempted one-pot reactions using excess cupric bromide in ethylene glycol-dioxan¹⁰ and bromine-ethylene glycol¹¹ gave a mixture of products. On the other hand, reaction of 3-pentanone with phenyltrimethylammonium tribromide and excess of ethylene glycol in tetrahydrofuran at room temperature yielded the bromoacetal 17 in 90% yield. Further work which was carried out to examine the scope and utility of this one-pot α -bromoacetalization reaction is dealt with in detail in Chapter II (Part B) of this thesis. All our attempts to effect the dialkylation of diethylmalonate 18 ($Y = COOEt$) with the bromoacetal 17 were futile, presumably due to the steric hindrance caused by the bulky ketal groups. In the light of similar observations made in several experiments in this direction, further work along this route was given up. Efforts to bring about the union of two five-carbon units of 17 through a Grignard reaction on ethyl formate (21) also proved equally fruitless.

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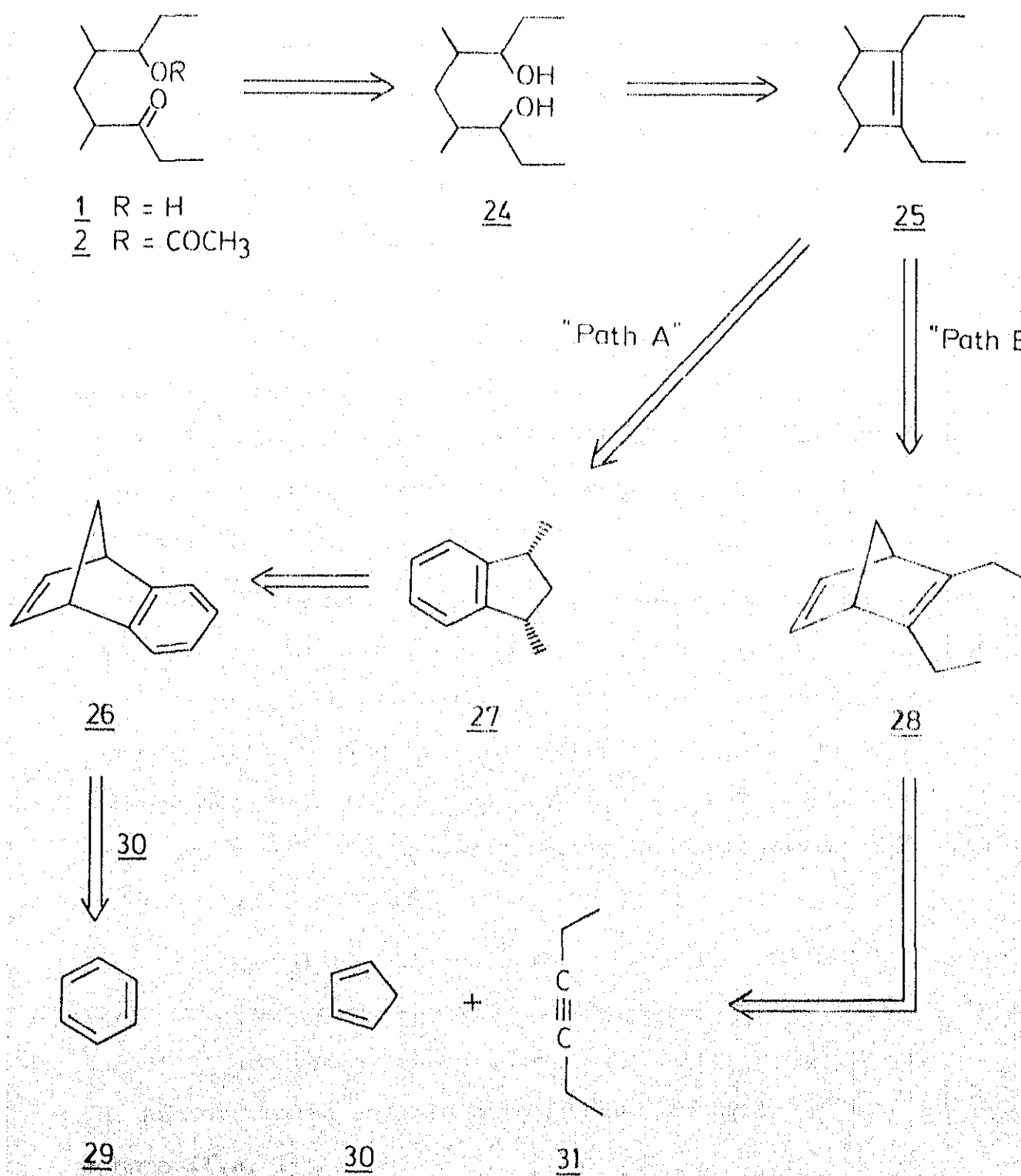
An alternative route that was envisaged would involve 2,4-dicyanopentane (20) as an important intermediate. This was achieved in three simple steps in the place of the circuitous route reported.¹² Reduction of acetylacetone with sodium borohydride yielded 2,4-pentanediol (22) as a mixture of racemic and meso isomers in 80% yield.¹³ In this reduction, the borate esters formed could be used to separate the meso and racemic forms. The borate ester formed from the racemic mixture is easily hydrolysed to the diol whereas, the cyclic meso-borate ester 23 is more resistant to hydrolysis. The meso diol was the major product of the reaction with only very small amount of the racemic mixture. The diol 22 was converted to 2,4-dichloropentane in quantitative yield.¹³ The dichloropentane was transformed into 2,4-dicyanopentane (20) in good yield (70%) using the known procedure for the conversion of secondary chlorides into nitriles.¹⁴ The Grignard reaction with two equivalents of ethyl magnesium bromide (19, X = Br) was performed on this meso-2,4-dicyanopentane (20) which did not proceed smoothly as expected. Several modifications were tried to carry out this reaction, which proved fruitless. At this stage, further work along this route was abandoned.

Another antithetic analysis of the target molecule revealed a more promising route in terms of stereochemical control at C-4 and C-6 and the overall strategy is described in Scheme II.A.4.

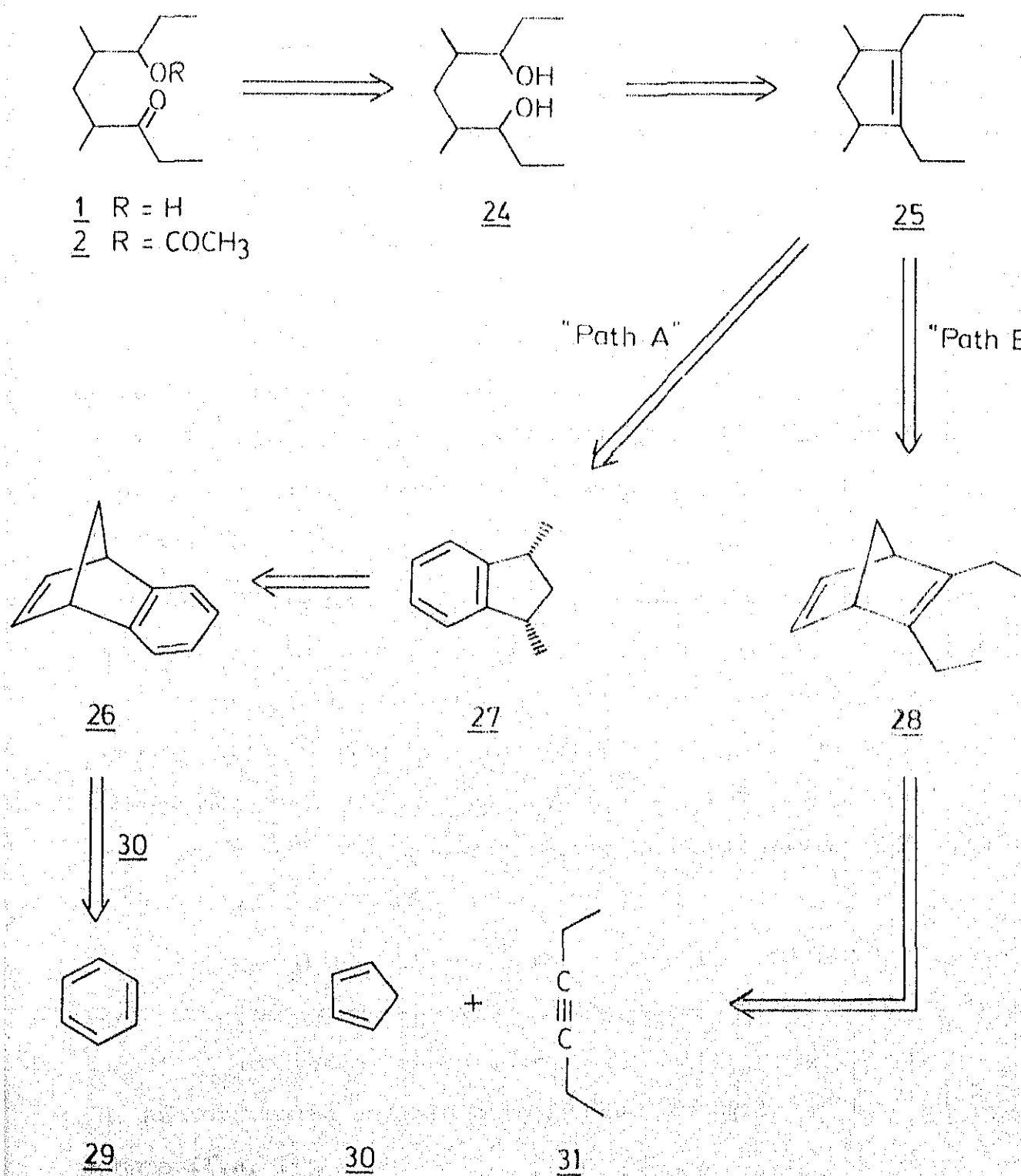
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Scheme II.A.4



Scheme II-A-4



The preliminary consideration of the two strategies revealed 'path B' to be simple in terms of the molecular framework manipulation, provided the cycloaddition reaction can be performed in decent yields. Since 3-hexyne (31) as such is an inactive dienophile, we tried to find out a suitable six carbon 3-ene or 3-yne system, activated by groups such as carbonyl at 2-position. A quick search in the literature indicated the scarcity of such dienophiles due to the difficulties encountered in their preparation. Hence, our initial attempts were focussed on adding 3-hexyne (31) onto cyclopentadiene (30). As anticipated, this cycloaddition was difficult to perform and under a variety of thermal conditions no useful product could be obtained.

The synthetic strategy which finally culminated in the synthesis of the target molecule, started with the facile [4+2] cycloaddition of cyclopentadiene (30) and benzyne (29), which was generated in situ to furnish benzonorbornadiene (26). Of all the methods, the one used by Friedman and Logullo was found to be the best¹⁵ and 26 was prepared conveniently in fair yield (60%) using this method.

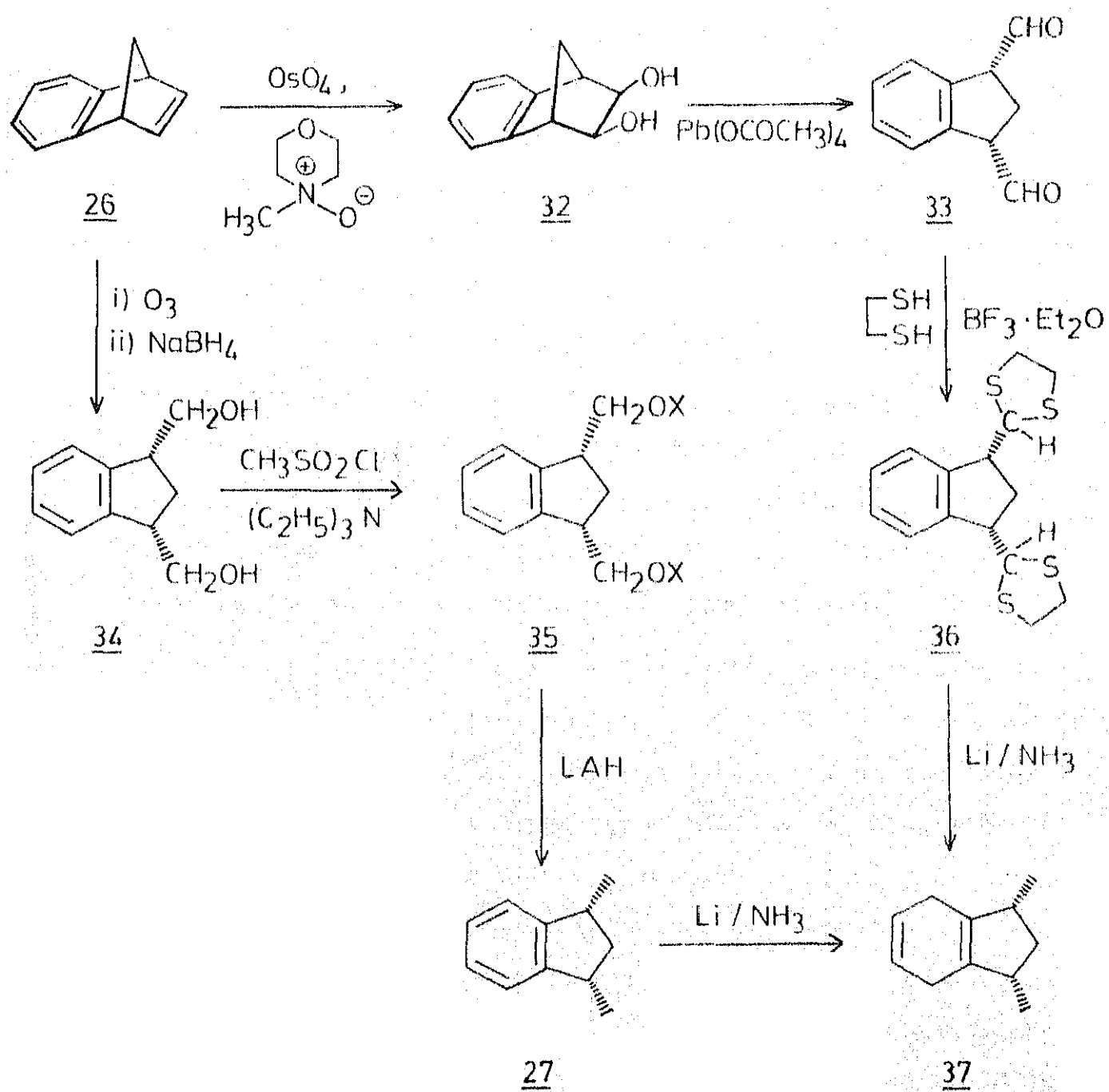
The key intermediate in this route is 1,3-dimethylindane (27). The methods that exist in the literature for the synthesis of 27 are rather circuitous¹⁶ or suffer from low yields.¹⁷ The present route envisaged to synthesize 27 is summarized in Scheme II.A.5.

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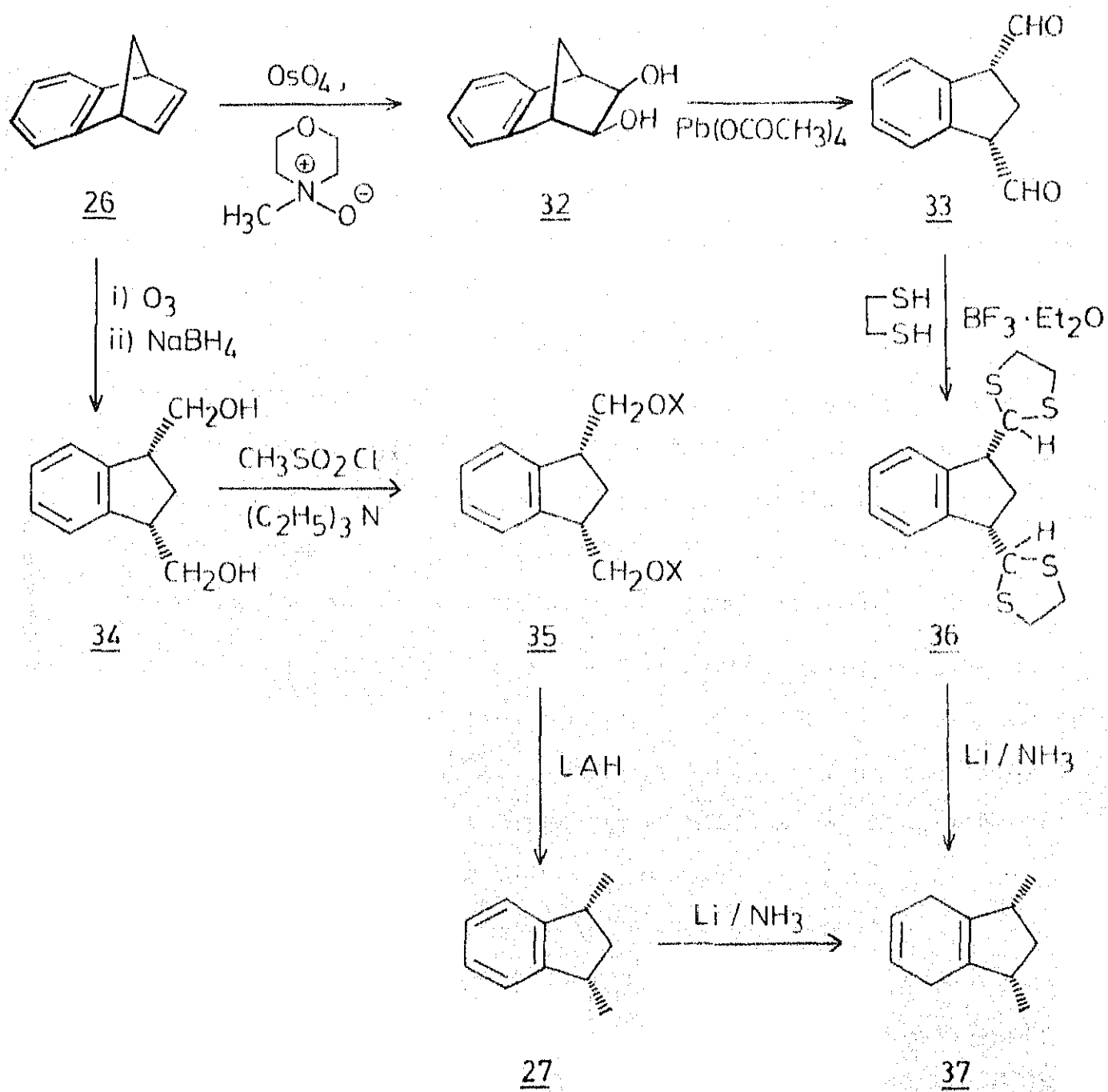
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Scheme II·A·5



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The dialdehyde 33 could be synthesized directly from 26 by a variety of procedures available in the literature for the cleavage of carbon-carbon double bonds. When benzonorbornadiene was treated with sodium metaperiodate and catalytic amount of osmium tetroxide, in 1:1 water-THF system (Lemieux-Johnson procedure),¹⁸ although a fairly clean reaction took place, it was difficult to isolate the pure product after extractive work-up. Ogino and Mochizuki have reported the selective oxidation of olefins to 1,2-diols or aldehydes, using potassium permanganate and benzyltriethylammonium chloride in dichloromethane, depending upon the pH of the aqueous solution used for cleaving the organomanganese intermediate.¹⁹ The compound 26 on oxidation under these conditions proceeded fairly smoothly but the isolation of the dialdehyde 33 was complicated by decomposition during the process of concentration.

Having failed in the isolation of the dialdehyde 33 in the one-step oxidative cleavage, the olefin 26 was subjected to cis-hydroxylation using catalytic amount of osmium tetroxide in the presence of N-methylmorpholine-N-oxide in aqueous acetone²⁰ to obtain the diol 32 (93%), m.p. 168-169°C. When the diol 32 was treated with lead tetraacetate at room temperature in benzene, a clean reaction occurred in five minutes to afford a pale yellow oil (85%), which was identified as 1,3-dialdehyde 33 based on the spectral data. The reduction of the aldehydic groups to the methyl groups would furnish the key intermediate, 1,3-dimethylindane (27).

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The usual Wolff-Kishner reduction was observed to be too harsh for this sensitive dialdehyde 33. Hence it was decided to convert the dialdehyde to the corresponding dithioacetal. When 33 was treated with two equivalents of 1,2-ethanedithiol in the presence of boron trifluoride etherate in dichloromethane at room temperature, the dithioacetal 36 was obtained in excellent yield (90%). With a view to doing two operations in one pot, namely, hydrogenolysis of the dithioacetals and the reduction of the aromatic ring, the dithioacetal 36 was subjected to a dissolving metal reduction in the presence of a large excess of lithium in liquid ammonia containing alcohol as a proton source. Reaction under these conditions afforded a mixture of two compounds as major products. One of the compounds was identified as the desired dihydrodimethylindane (37) and the other product as arising from the partial hydrogenolysis of the thioacetal moiety. Attempts to force the reaction to go to completion by using larger excess of lithium and longer reaction time proved to be futile. Other methods which were being studied simultaneously to convert benzonorbornadiene (26) to the hydrocarbon 27 gave encouraging results.

When benzonorbornadiene (26) was subjected to ozonolysis in dichloromethane at -78°C , followed by reduction with excess of sodium borohydride²¹ in 50% cold aqueous ethanol, 1,3-bis-(hydroxymethyl)indane (34) was obtained in good yield (70%), m.p. $99-100^{\circ}\text{C}$. The IR spectrum showed an absorption at 3290 cm^{-1} ,

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typical of the hydroxyl group. The PMR spectrum showed a multiplet ranging between δ 1.64-2.72 (2H) which can be assigned to the methylene protons and a singlet at 2.18 (2H, D_2O exchangeable) corresponding to the hydroxyl protons. The methine protons indicated a multiplet at 3.44 (2H) and the methylene protons appeared as a doublet at 3.92 (4H). The aromatic protons traced a singlet at 7.3 (4H) (Fig. II.A.1). The mass spectrum showed the molecular ion peak at m/e 178.

Next, the hydroxyl group has to be suitably transformed, which on reduction would be able to furnish the dimethylindane (27). Olah *et al.* have reported the transformation of alcohols to iodides using chlorotrimethylsilane and sodium iodide in acetonitrile in quantitative yields.²² This method appeared to be a mild one and the diol 34 was treated with two equivalents of sodium iodide and two equivalents of chlorotrimethylsilane under nitrogen atmosphere. Surprisingly, no diiodo compound 35 ($X = I$) was found to be formed. This reaction, which is a general reaction with simple alcohols seems to fail in the case of dihydroxy compounds. This observation was further confirmed by the fact that, in separate experiments 1,5-pentanediol and 1,6-hexanediol under the same conditions did not give the diiodides.

We next focussed our attention to prepare the ditosylate 35 ($X = OTs$) from the diol 34. When the diol 34 was treated with freshly recrystallised *p*-toluenesulphonyl chloride in

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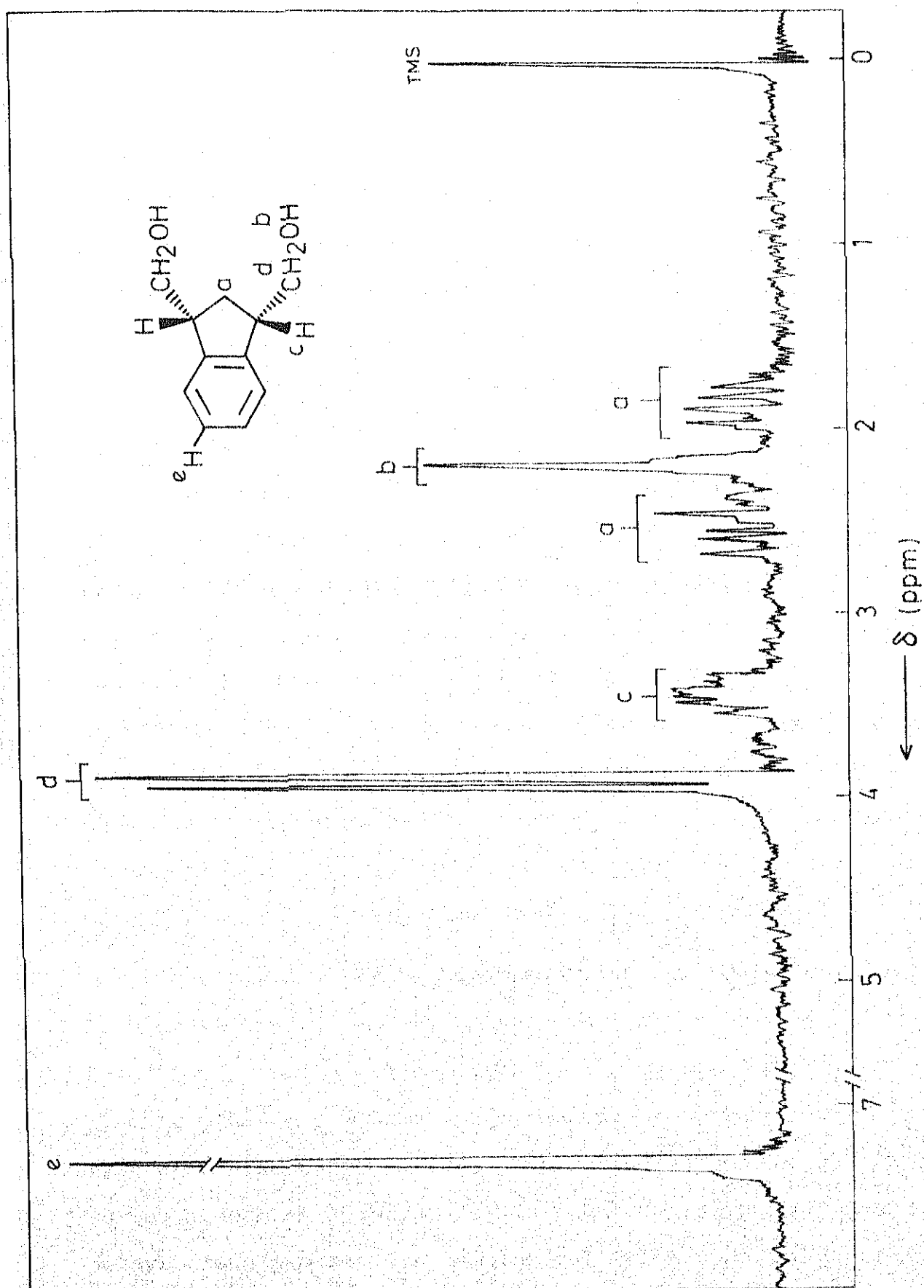


Fig. II-A-1 ^1H NMR spectrum (80 MHz) of **34**.

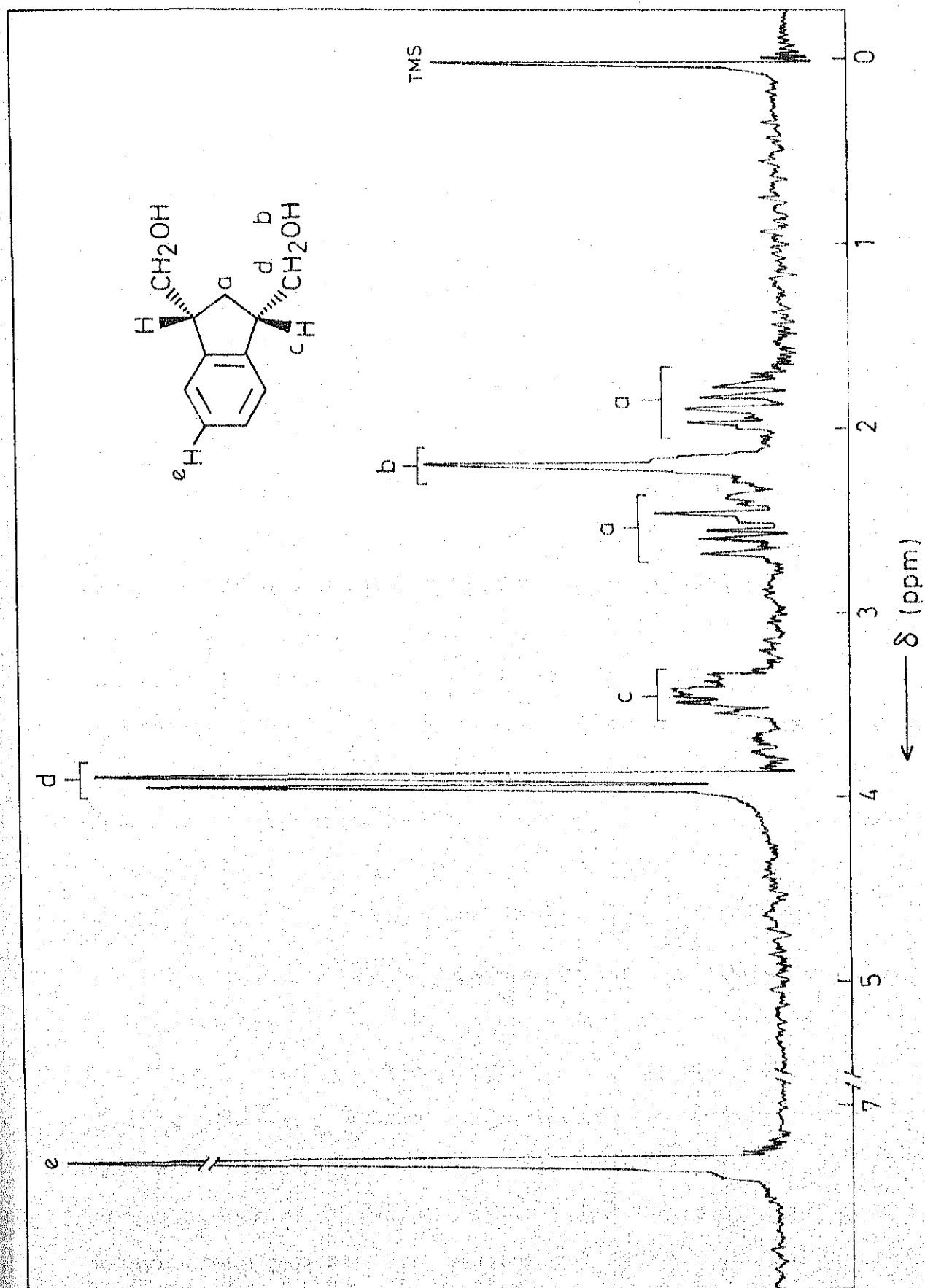


Fig. II-A-1 ^1H NMR spectrum (80 MHz) of 34.1.

pyridine at 0°C, a white solid, m.p. 105-106°C was obtained in poor yield. Efforts to improve the yield by various manipulations of the reaction conditions did not give the desired ditosylate derivative in satisfactory yields. However, treatment of the diol 34 with two equivalents of methanesulphonyl chloride and triethylamine in dichloromethane at ca. -20°C yielded the dimesylate 35 (X = OMs), m.p. 134-135°C in very good yield (95%).

The dimesylate 35 (X = OMs) on reduction with eight equivalents of lithium aluminium hydride in refluxing ether for two hours afforded 1,3-dimethylindane (27) in good yield (80%), b.p. 80-82°C (7 mm) [lit.¹⁷ b.p. 202.3°C (740 mm)]. The PMR spectrum showed a sharp doublet at δ 1.3 (6H, J = 7 Hz) assigned to the methyl group protons. The methylene protons showed a multiplet centred at δ 2.46 (2H) and yet another multiplet was shown by the methine protons centred at 3.1 (2H). The aromatic protons appeared as a singlet at 7.15 (4H) (Fig.II.A.2). The mass spectrum of 27 showed the molecular ion peak at m/e 146.

The compound 27 on treatment with ten equivalents of lithium in liquid ammonia, followed by six equivalents of ethanol gave dihydrodimethylindane (37) in 95% yield, b.p. 62-64°C (7 mm). The IR spectrum of 37 showed absorption at 1650 cm⁻¹ typical of the carbon-carbon double bond. The PMR spectrum showed a doublet at δ 1.0 (6H, J = 6 Hz) corresponding to the methyl group protons. A complex multiplet appeared between

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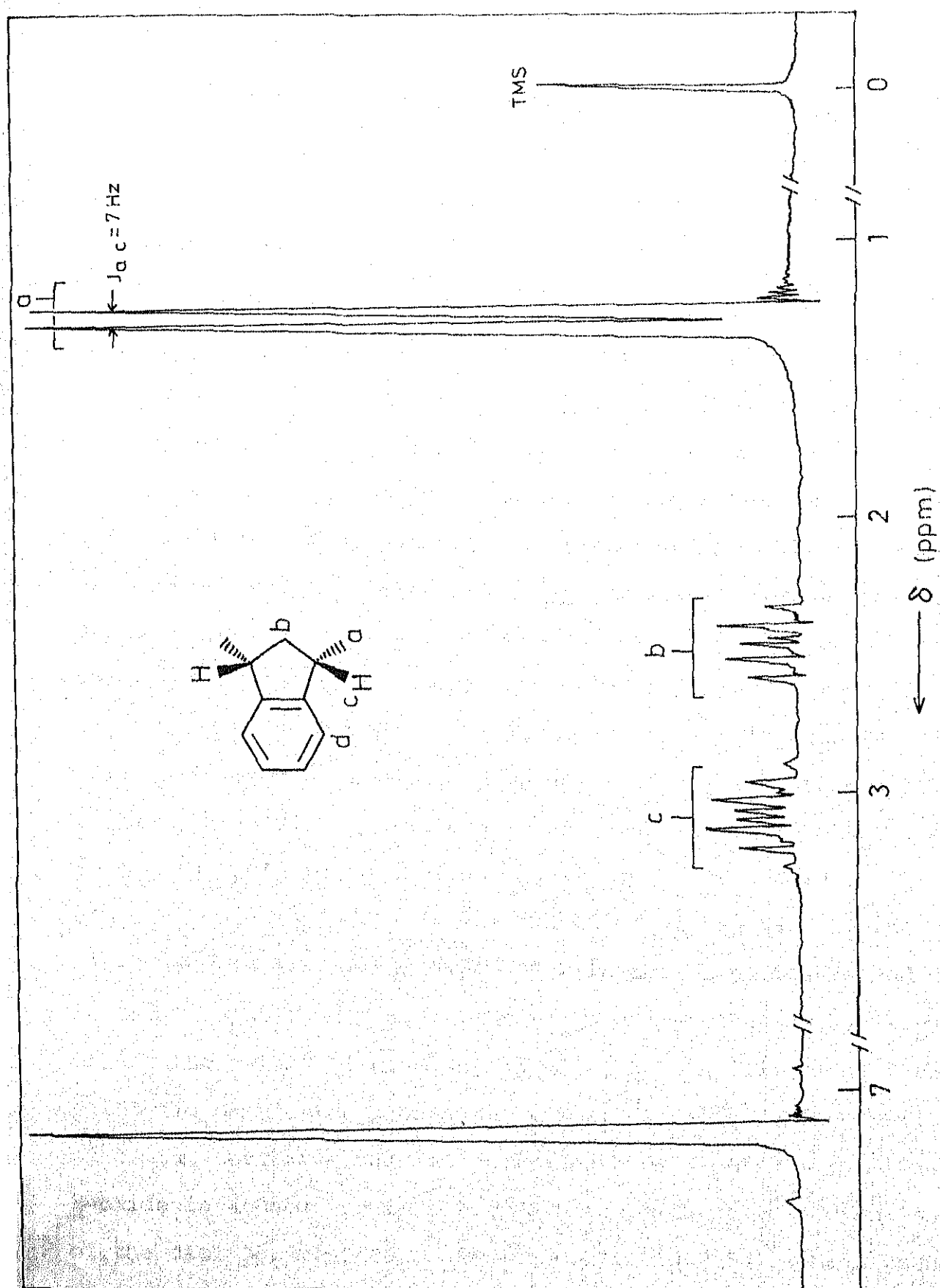


Fig. II.A.2 ^1H NMR spectrum (100 MHz) of **27**.

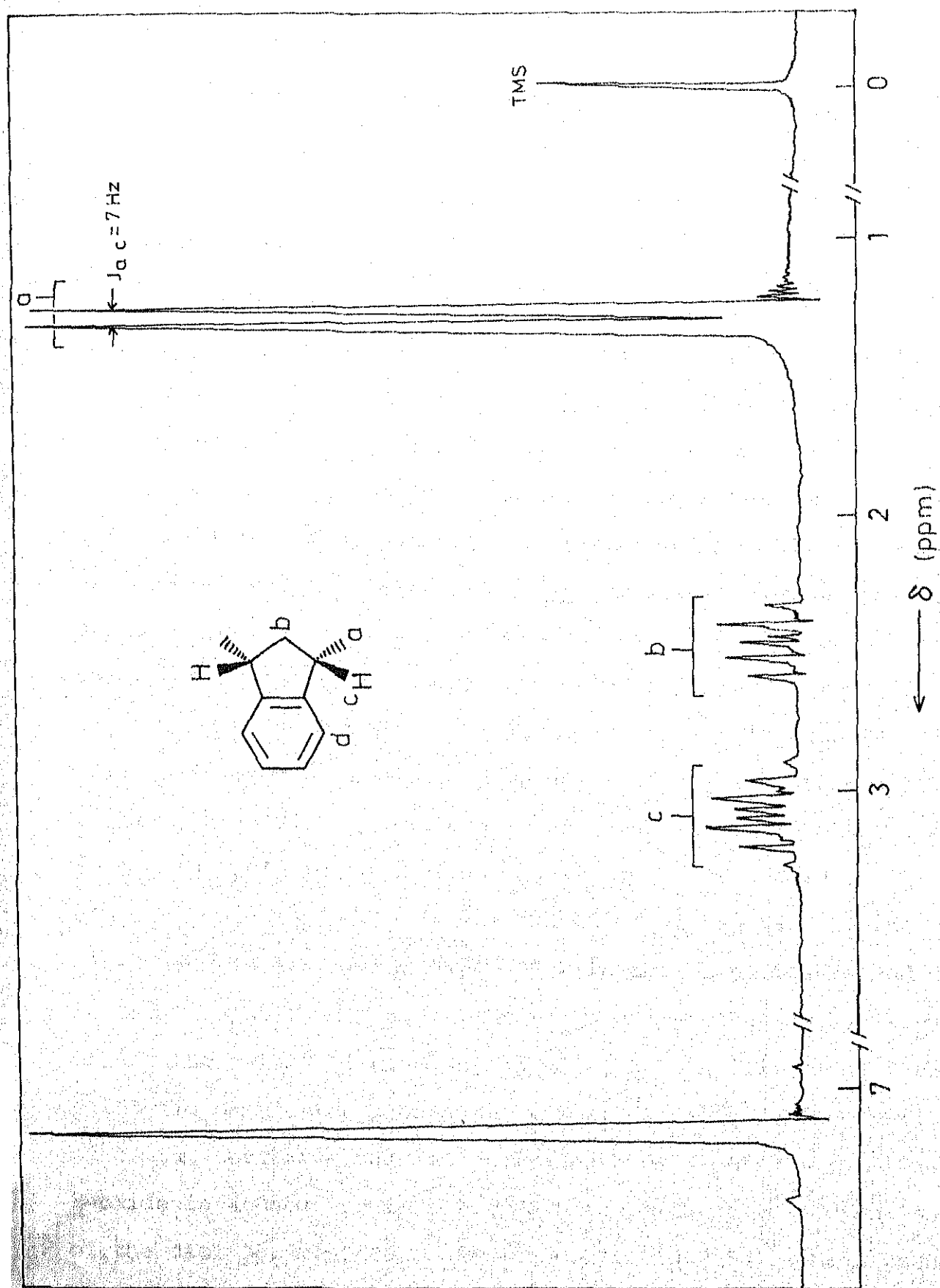


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2.16 and 2.9 (8H) due to the six methylene protons and two methine protons. The vinylic protons produced a singlet at 5.74 (2H) (Fig. II.A.3). The mass spectrum indicated the molecular ion peak at m/e 148.2.

As encountered earlier, there are two strategies at our disposal. The disubstituted double bond can be selectively cleaved either directly or through the formation of the diol as outlined in Scheme II.A.6. Initially, we directed our attention to the oxidative cleavage of the disubstituted double bond to yield the dialdehyde 39, which can be further reduced to give another key intermediate 25, in the pheromone synthesis. Exposure of the diene 37 to Johnson-Lemieux reaction conditions¹⁸ using osmium tetroxide and sodium metaperiodate led to a mixture of products. Treatment of 37 with potassium permanganate solubilized in dichloromethane by means of benzyltriethylammonium chloride at 0°C, followed by cleaving the manganate ester using an aqueous solution of sodium acetate and acetic acid at pH 3,¹⁹ did not yield any of the required dialdehyde 39. Attempted cis-hydroxylation of the diene 37 with potassium iodate and iodine in acetic acid at reflux followed by alkaline hydrolysis²³ also failed to give any cis-diol 38. Application of the catalytic osmylation procedure of Kelly²⁰ using 0.1 equivalent of osmium tetroxide and 1.3 equivalents of N-methylmorpholine-N-oxide in aqueous acetone for 80 h resulted in the formation of the diol 38, m.p. 99-100°C in poor yield (25%). More than

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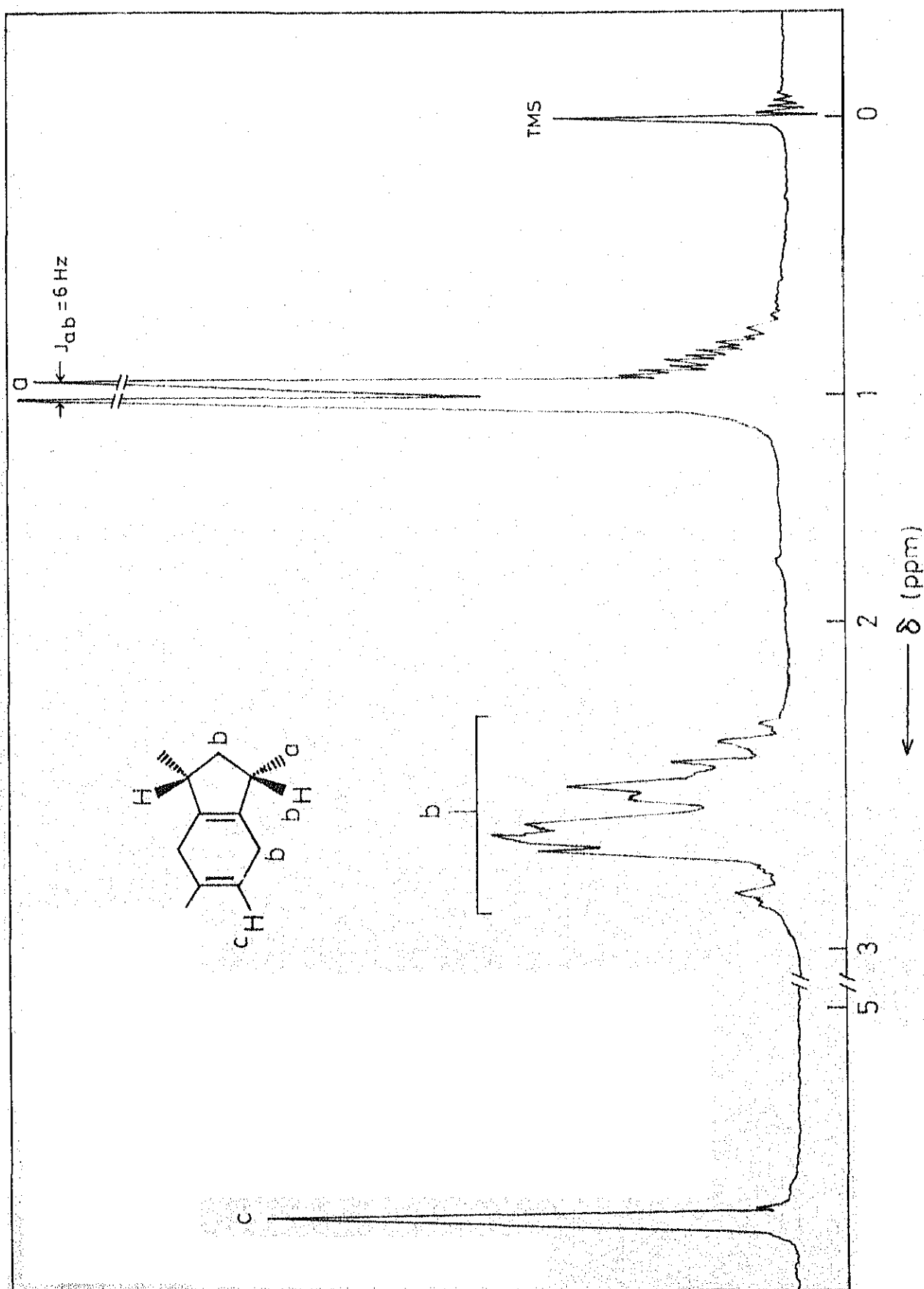
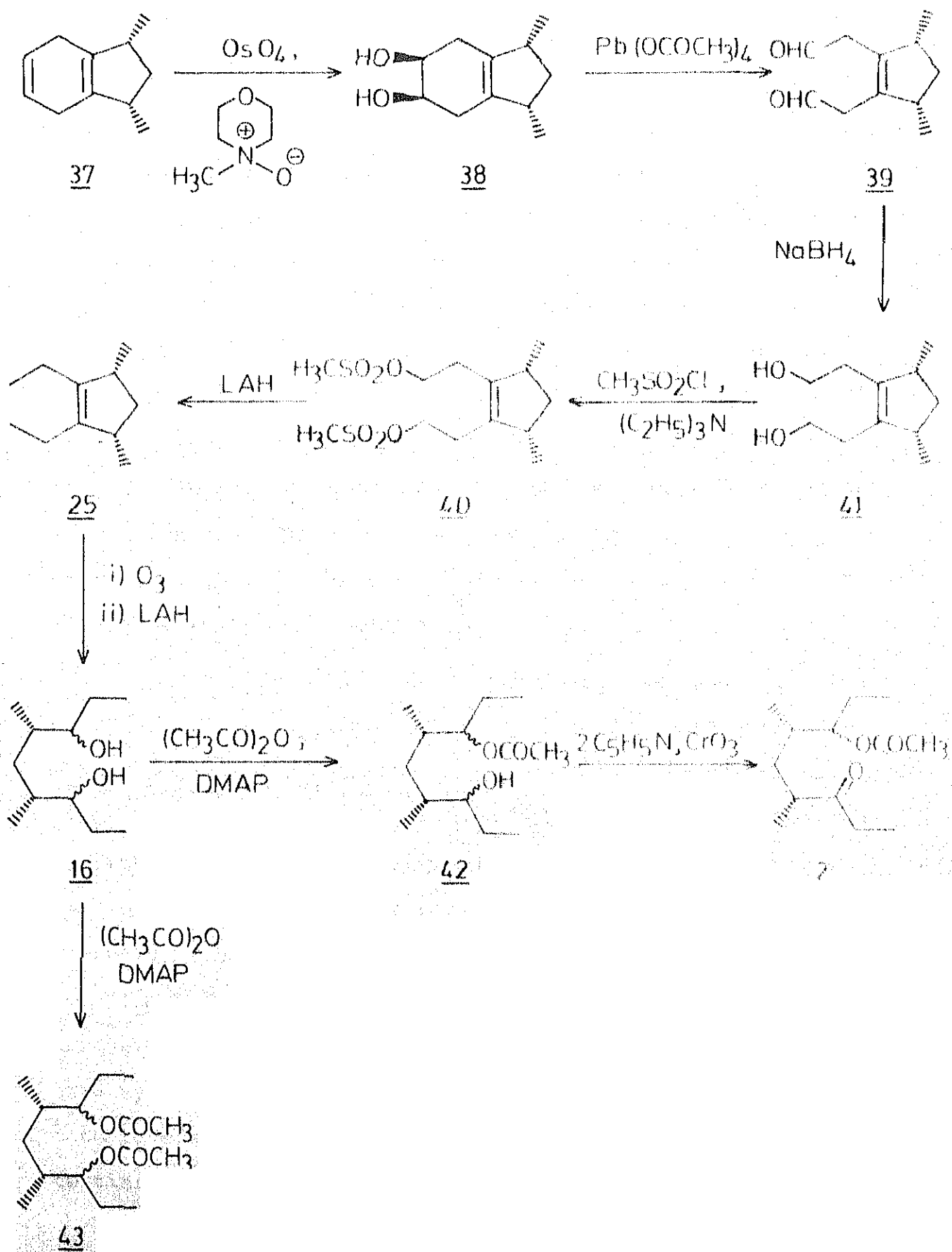


Fig. II-A-3 ^1H NMR spectrum (100 MHz) of 37.

Scheme II-A-6



60% of the starting material was recovered unchanged. Several variations were attempted to force the reaction to completion, such as increasing the amount of osmium tetroxide, carrying out the reaction at a higher temperature, changing the solvent system to tert-butanol-water, tert-butanol-tetrahydrofuran-water and using stoichiometric amount of osmium tetroxide-pyridine, without much success. The IR spectrum of 38 showed a strong absorption at 3330 cm^{-1} typical of the hydroxyl group. The PMR spectrum showed a doublet at $\delta 0.98$ (6H, $J = 6\text{ Hz}$) corresponding to the methyl group protons and a broad multiplet between 1.8 and 2.7 (8H) due to the methylene, the methine and the hydroxyl group protons. The methine protons appeared as a multiplet centred at $\delta 3.96$ (2H) (Fig. II.A.4). The mass spectrum showed a molecular ion peak at m/e 182.

The poor yield obtained in the above reaction prompted us to examine the cis-hydroxylation reaction with different reagents, to substitute the expensive and toxic osmium tetroxide. Since the reaction was proceeding only to 30% completion and major amount of the starting material was being recovered, it was felt that the use of osmium tetroxide was not justified. Recently, Sargent and Sala have prepared and used tetrabutylammonium permanganate for oxidation of aromatic aldehydes and aromatic hydrocarbons.²⁴ Schäfer and coworkers have used benzyltriethylammonium permanganate for the oxidation of benzylic methylene and methine groups to the corresponding ketonic or tertiary hydroxyl functions.^{25,26} However, such quaternary

60% of the starting material was recovered unchanged. Several variations were attempted to force the reaction to completion, such as increasing the amount of osmium tetroxide, carrying out the reaction at a higher temperature, changing the solvent system to tert-butanol-water, tert-butanol-tetrahydrofuran-water and using stoichiometric amount of osmium tetroxide-pyridine, without much success. The IR spectrum of 38 showed a strong absorption at 3330 cm^{-1} typical of the hydroxyl group. The PMR spectrum showed a doublet at $\delta 0.98$ (6H, $J = 6\text{ Hz}$) corresponding to the methyl group protons and a broad multiplet between 1.8 and 2.7 (8H) due to the methylene, the methine and the hydroxyl group protons. The methine protons appeared as a multiplet centred at $\delta 3.96$ (2H) (Fig. II.A.4). The mass spectrum showed a molecular ion peak at $m/e\ 182$.

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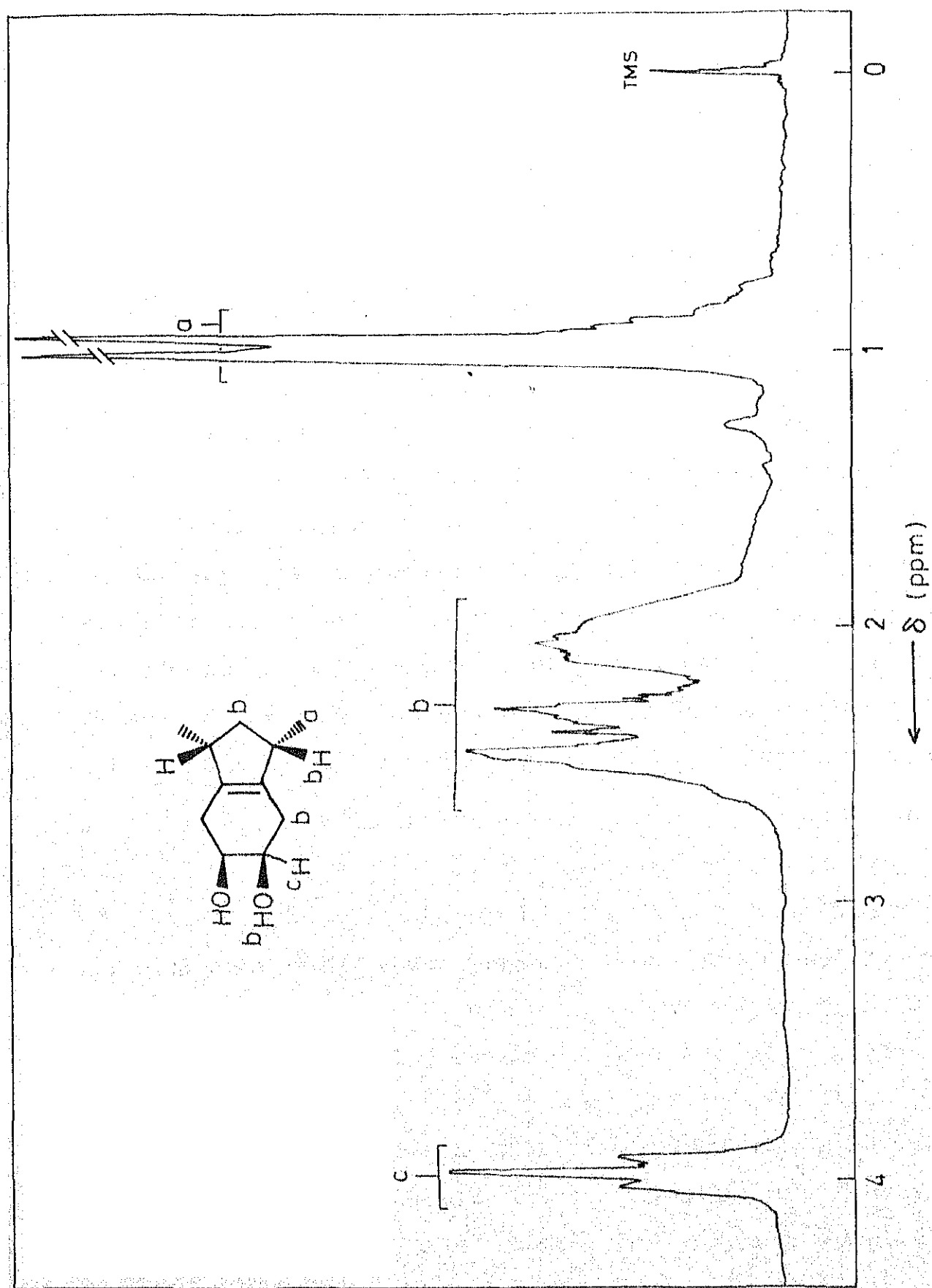


Fig. II-A-4 ^1H NMR spectrum (100 MHz) of **38**.

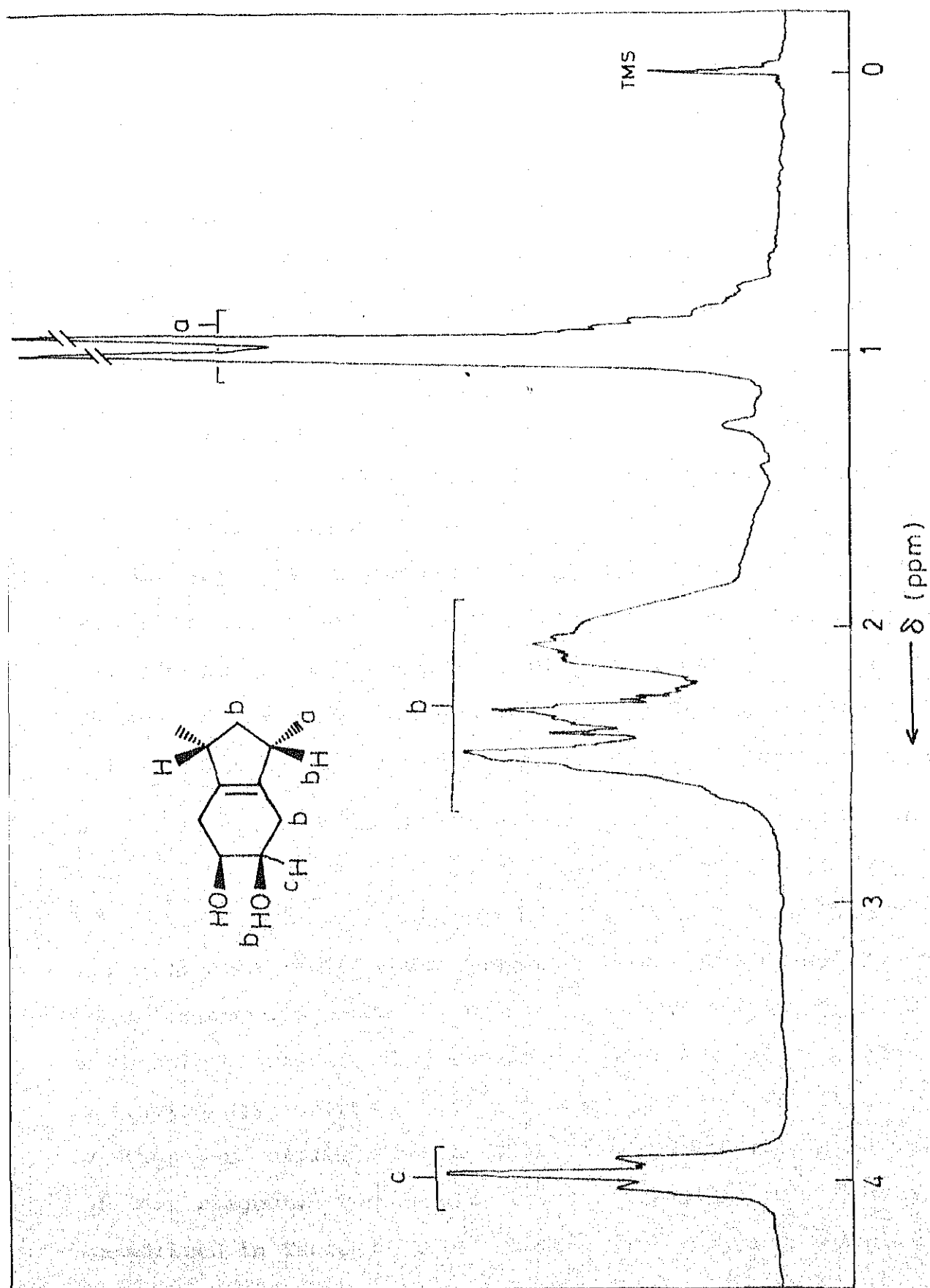


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ammonium permanganate salts have not been employed so far for the hydroxylation of double bonds. During our investigation to effect the cis-hydroxylation of the double bond, we developed a mild and stable quaternary ammonium permanganate reagent, namely, cetyltrimethylammonium permanganate, a purple crystalline solid.

Cetyltrimethylammonium permanganate (CTAP) was prepared by adding a saturated solution of cetyltrimethylammonium bromide to an aqueous potassium permanganate solution, with efficient stirring at room temperature. The purple fluffy precipitate was filtered, washed thoroughly with water and dried in vacuo over phosphorus pentoxide for 3 h. This permanganate salt decomposed above 85°C and could be stored in the refrigerator for a prolonged period of time without loss of activity.

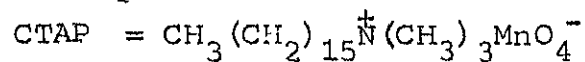
Treatment of olefins with a solution of CTAP in dichloromethane, at 20°C, yielded the corresponding cis-dihydroxy compounds in good yield in 1-4 h. The isolation of the product could be done either under anhydrous conditions or by treatment with 10% aqueous sodium hydroxide solution, followed by extraction with chloroform. Equally good results were obtained when the oxidation was carried out in aqueous tert-butanol. Several olefins were oxidized to the diols to test the scope and utility of this reagent. The results of this oxidation with CTAP are summarized in Table II.A.1. Olefins with aliphatic substituents

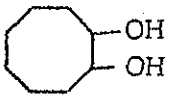
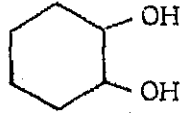
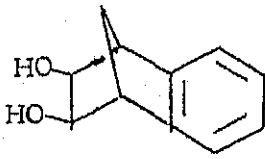
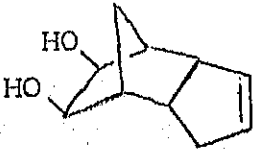
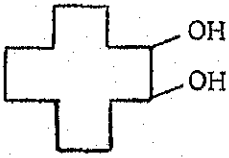

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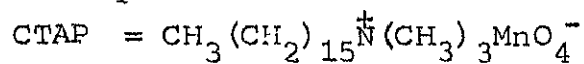
Table II.A.1. cis-Hydroxylation of the Double Bonds Using
One Equivalent of CTAP

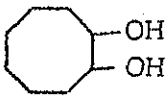
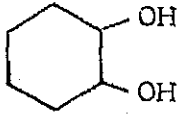
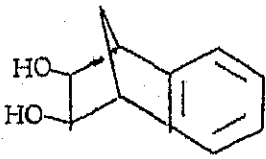
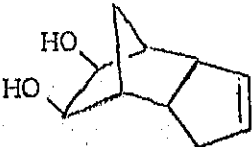
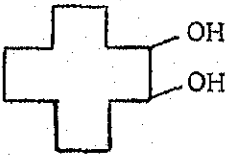



No.	Substrate	Reaction time (h)	Product	Yield (%)	m.p. (°C)	Refer- ence
1.	Cyclooctene	1		73	78-79	27
2.	Cyclohexene	1		86	97-98	28
3.	Benzonor- bornadiene	3		73	168-69	-
4.	<u>endo</u> -Dicyclo- pentadiene	4		86 ^a	48-49	19
5.	Cyclododecene	5		65 ^a	157-58	29
6.	1-Octene	2		85	-	30

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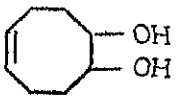
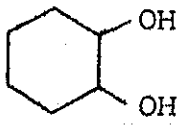
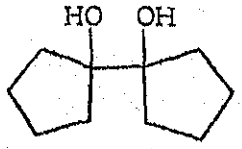
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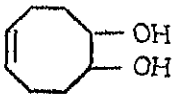
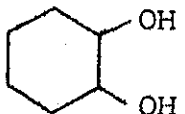
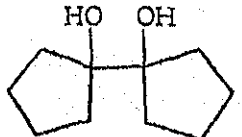
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Table II.A.1 (contd.)

No.	Substrate	Reaction time (h)	Product	Yield (%)	m.p. (°C)	Reference
7.	1,5-Cyclo-octadiene	1		35	105-6	31
8.	<u>trans</u> -Stilbene	1	C_6H_5CHO	70 ^a	-	-
9.	Hydroxybenzoin	0.5	C_6H_5CHO	97	-	-
10.	Benzopinacol	0.5	$C_6H_5COC_6H_5$	89	-	-
11.		24	No reaction	-	-	-
12.		24	No reaction	-	-	-

a, based on the recovery of the starting material.

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consistently gave good to excellent yields of the diols. The aromatic substrates were found to give rise to the aldehydes (entry 8). In order to check the ease with which the cis-1,2-diols would be cleaved to give rise to the aldehydes, experiments were carried out with hydroxybenzoin, benzopinacol, cis-1,2-cyclohexanediol and 1,1'-dihydroxybicyclopentane (entry 9, 10, 11 and 12). The aromatic diols were cleaved readily to yield the aldehydes and the aliphatic diols proved rather inert to the reagent.

Having successfully tested the efficiency of the reagent with a variety of olefins, the dihydrodimethylindane (37) was treated with CTAP. Unfortunately, the substrate 37 did not undergo any oxidation with this reagent, although a stable, mild and inexpensive reagent has been added to the arsenal of organic chemists, for effecting cis-hydroxylation of olefins under anhydrous conditions. The reasons for the total lack of reactivity of 37 towards CTAP and the inferior yields obtained in the hydroxylation of 37 with other reagents are still obscure.

Considerable efforts were expended to improve the yield of the dihydroxy compound 38 without much success. Nevertheless, further work on the synthesis was pursued with diol 38 obtained by catalytic osmylation reaction, followed by recycling the recovered starting material. Exposure of diol 38 to lead tetraacetate (1.2 equivalents) in benzene at room temperature for 0.25 h cleanly generated the dialdehyde 39. Since

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dialdehyde 39 was found to be quite unstable, it was immediately reduced with sodium borohydride in ethanol at 0°C, to yield the dihydroxy compound 41, m.p. 59-60°C, in 95% yield (overall yield of 85% from the diol 38). The IR spectrum of the diol 41 showed a broad absorption at 3350 cm^{-1} typical of the hydroxyl group. The PMR spectrum indicated a doublet at δ 1.0 (6H, $J = 7\text{ Hz}$) due to the methyl group protons, a multiplet between 2.04 and 2.8 (8H) corresponding to the methylene and the methine protons. The hydroxyl group appeared at 3.02 (2H) as a broad signal and a multiplet was traced between 3.54 and 3.8 (4H) due to the methylene protons α - to the oxygen atom (Fig. II.A.5). The mass spectrum showed the molecular ion peak at m/e 184.

The dihydroxy compound 41 was treated with two equivalents of methanesulphonyl chloride and triethylamine in tetrahydrofuran at -20°C for 2 h to yield the dimesylate 40 in excellent yield (91%). The PMR spectrum showed a doublet at δ 1.03 (6H, $J = 6\text{ Hz}$) corresponding to the methyl group protons. The methylene and the methine protons indicated a multiplet between 2.06 and 2.83 (8H). A singlet at 2.96 (6H) due to the methyl protons and a multiplet at 4.16 (4H) due to the methylene protons also appeared in the spectrum (Fig. II.A.6).

The reduction of the freshly prepared dimesylate 40 with lithium aluminium hydride in refluxing ether for 2 h furnished the hydrocarbon 25 in moderate yield (50%). A small increase in

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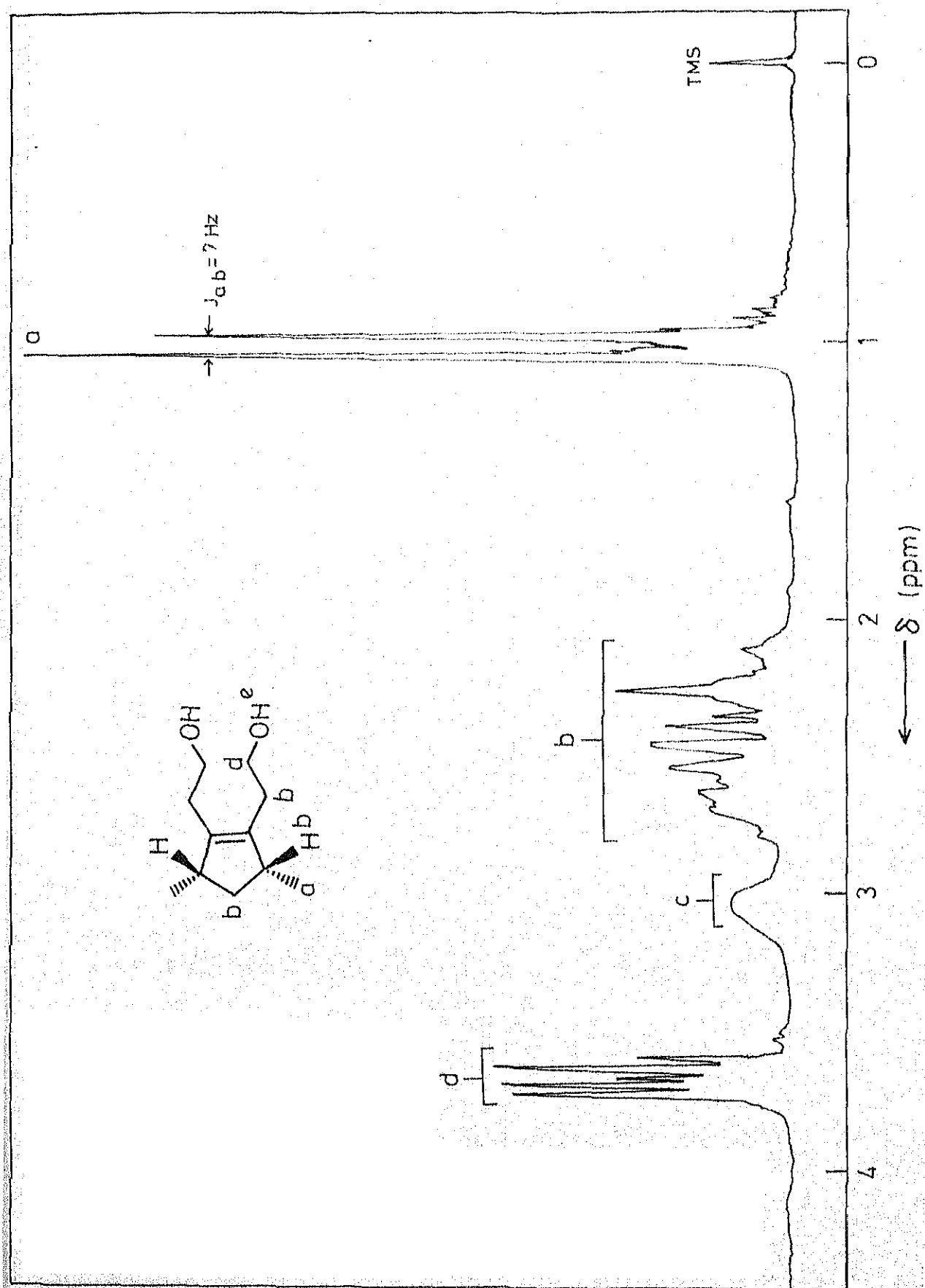


Fig. II-A-5 ^1H NMR spectrum (100 MHz) of 41.

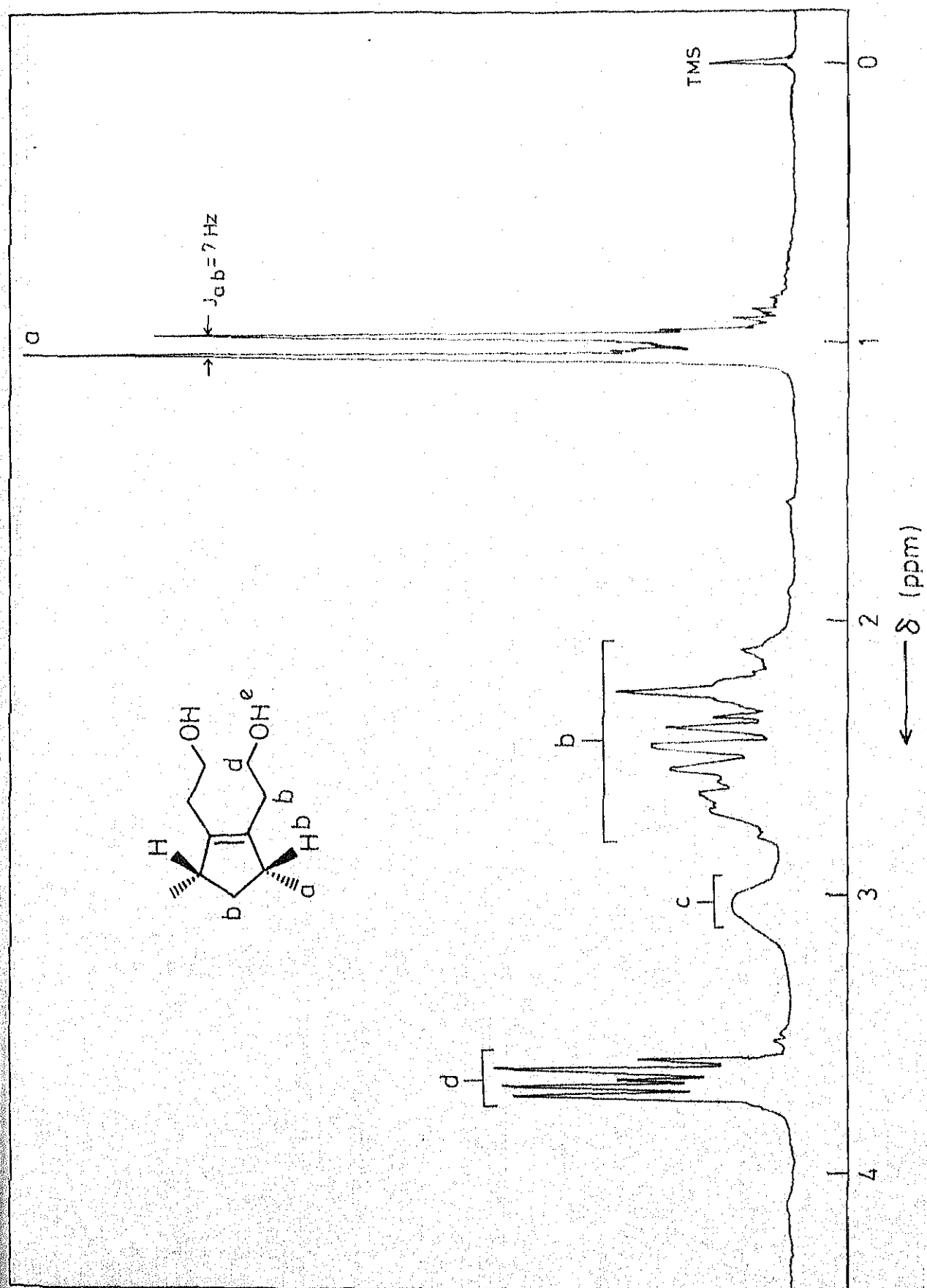


Fig. II-A-5 ^1H NMR spectrum (100 MHz) of 41.

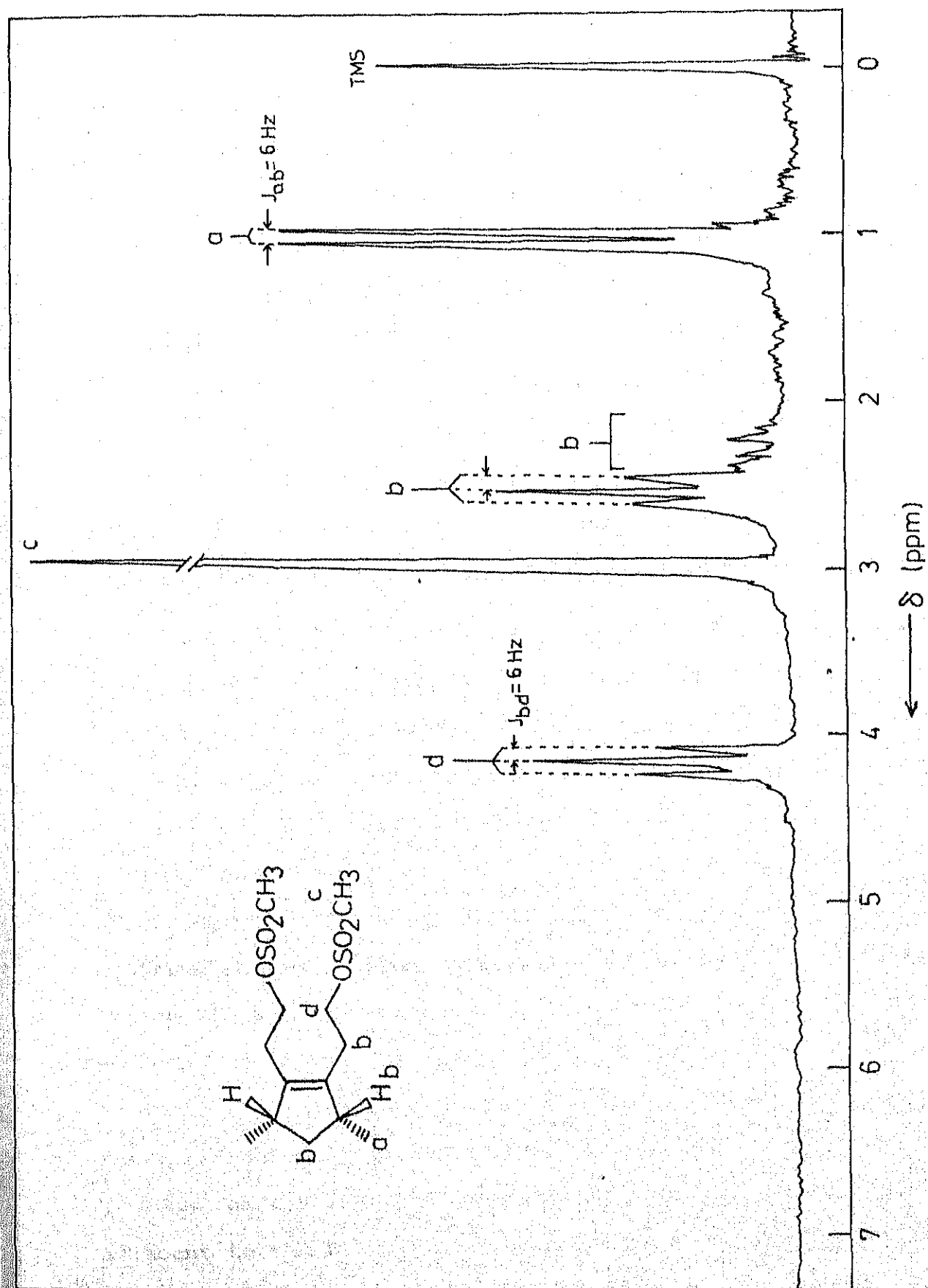


Fig. II-A-6 ^1H NMR spectrum (90 MHz) of 40.

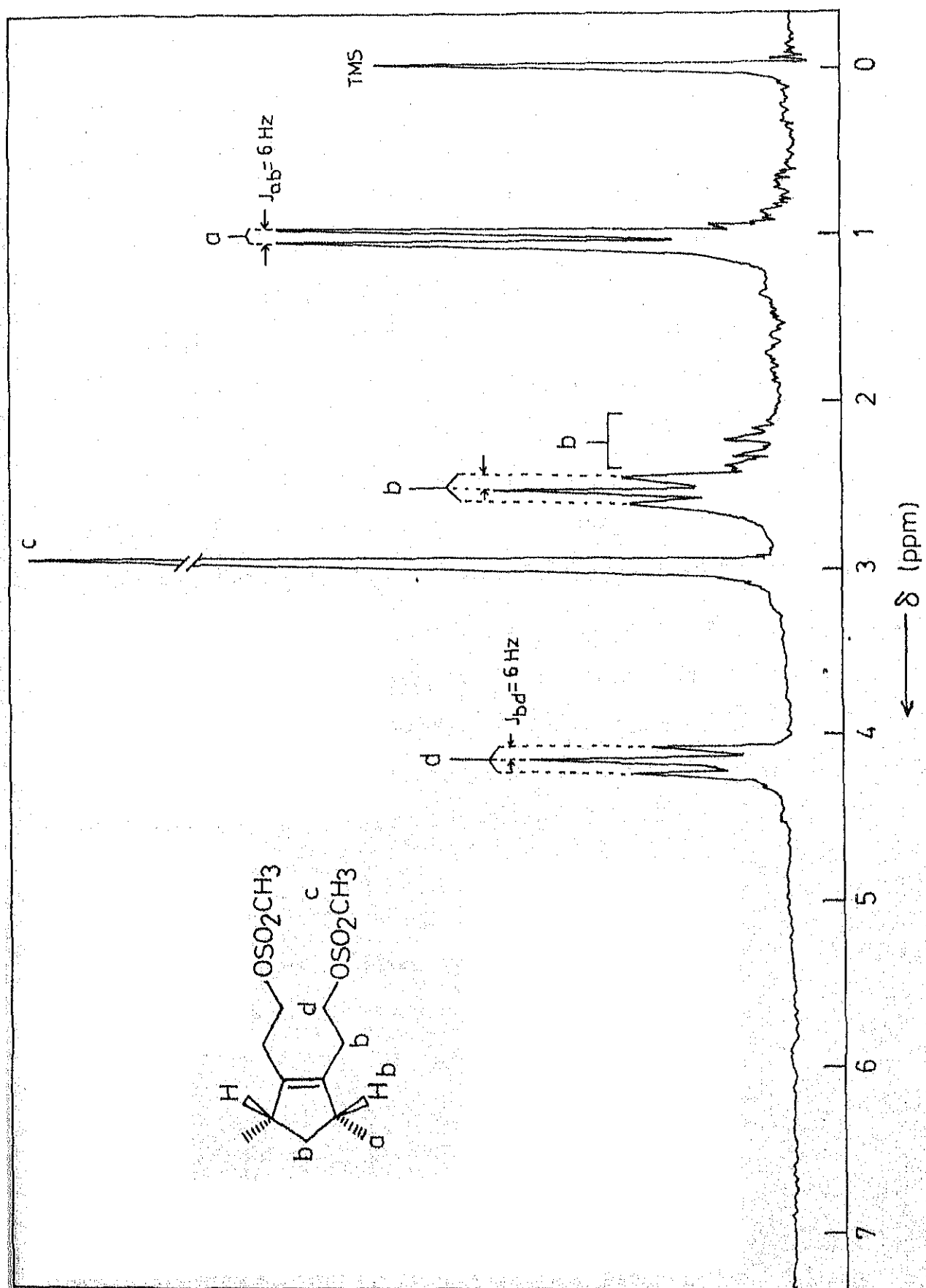


Fig. II-A-6 ^1H NMR spectrum (90 MHz) of **40**.

the yield (60%) was observed when the dimesylate 40 was quickly filtered through a short silica gel column before reduction. Traces of methanesulphonic acid that might be present in the unpurified mesylate could have caused polymerization of the product 25, thereby lowering the yield. The PMR spectrum showed a triplet at δ 0.91 (6H, $J = 7\text{Hz}$) corresponding to the methyl protons and a doublet at 0.98 (6H, $J = 7.5\text{ Hz}$) assigned to the methyl group protons. A multiplet appeared between 1.82 and 2.38 (6H) for the methylene protons and a quartet at 2.58 (2H, $J = 7.5\text{ Hz}$) due to the methine protons (Fig. II.A.7). The mass spectrum indicated the molecular ion peak at m/e 152.

The double bond cleavage of the hydrocarbon 25, a key intermediate in the pheromone synthesis, would furnish the desired molecular framework of Serricornin. Ozonolysis of the hydrocarbon 25 in dichloromethane at 0°C , followed by reduction of the ozonide in tetrahydrofuran with eight equivalents of lithium aluminium hydride at room temperature for 2 h yielded the dihydroxy compound 24 in excellent yield (92%). The IR spectrum showed a strong absorption at 3370 cm^{-1} indicative of the hydroxyl group. The PMR spectrum showed a broad signal between δ 0.6 and 1.1 (12H) corresponding to the methyl group protons. The methylene and the methine protons showed a broad multiplet between 1.1 and 1.8 (8H). The hydroxyl protons showed a signal at 1.9 (2H, D_2O exchangeable) and the methine protons adjacent to the hydroxyl group appeared as a broad multiplet between 3.1 and 3.5 (2H) (Fig. II.A.8).

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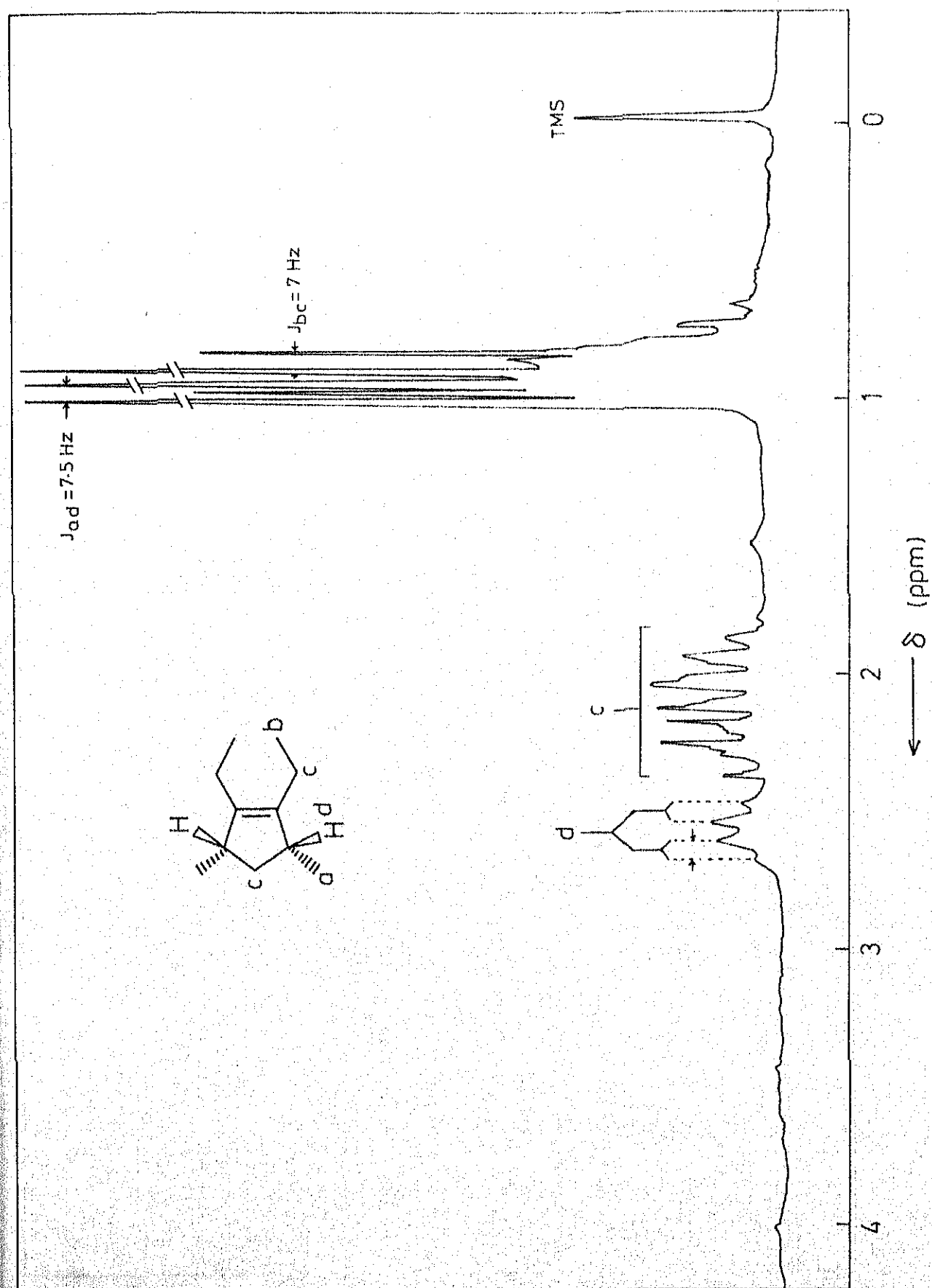


Fig. II.A.7 ^1H NMR spectrum (100 MHz) of **25**.

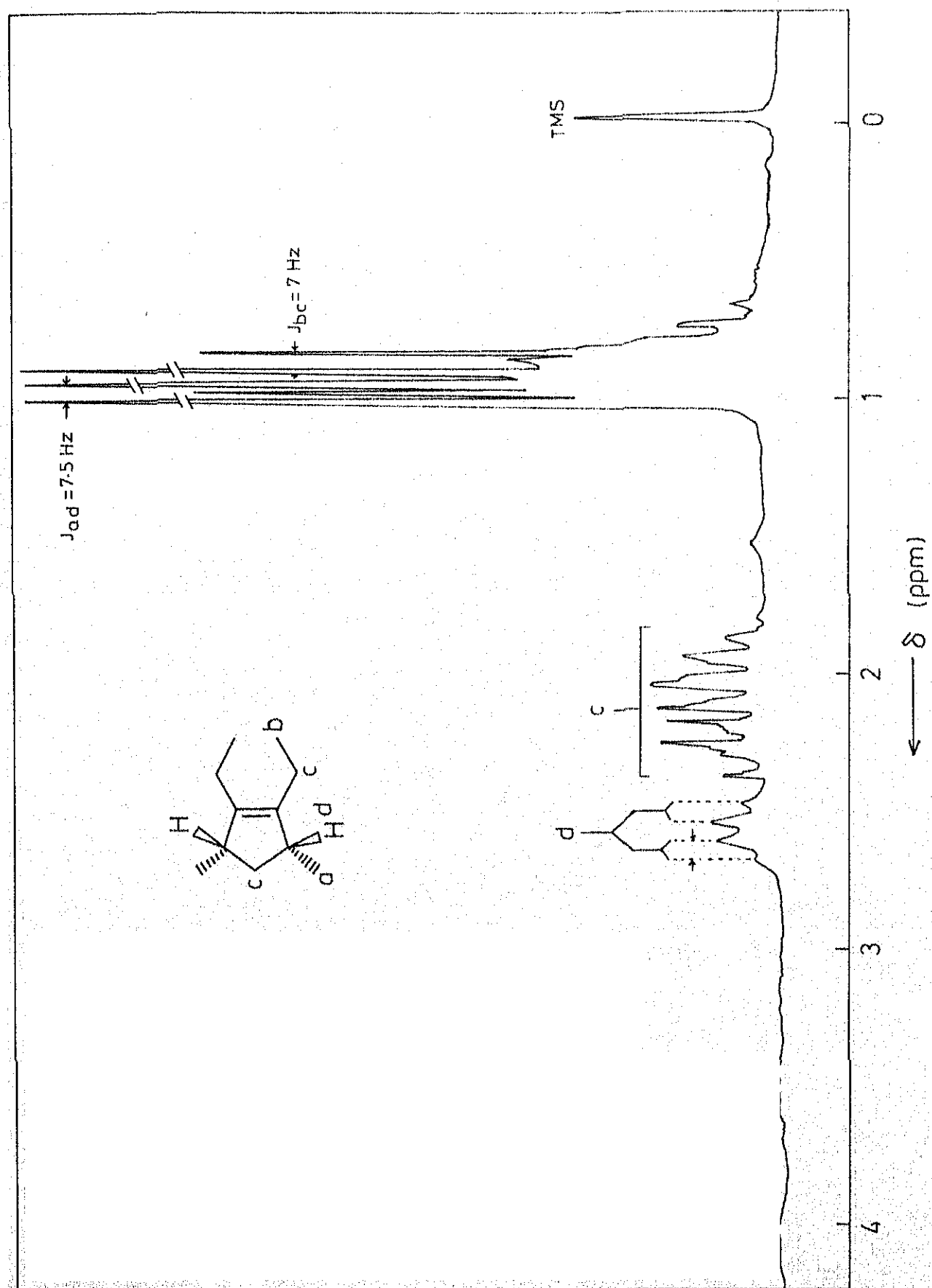


Fig. II.A.7 ^1H NMR spectrum (100 MHz) of **25**.

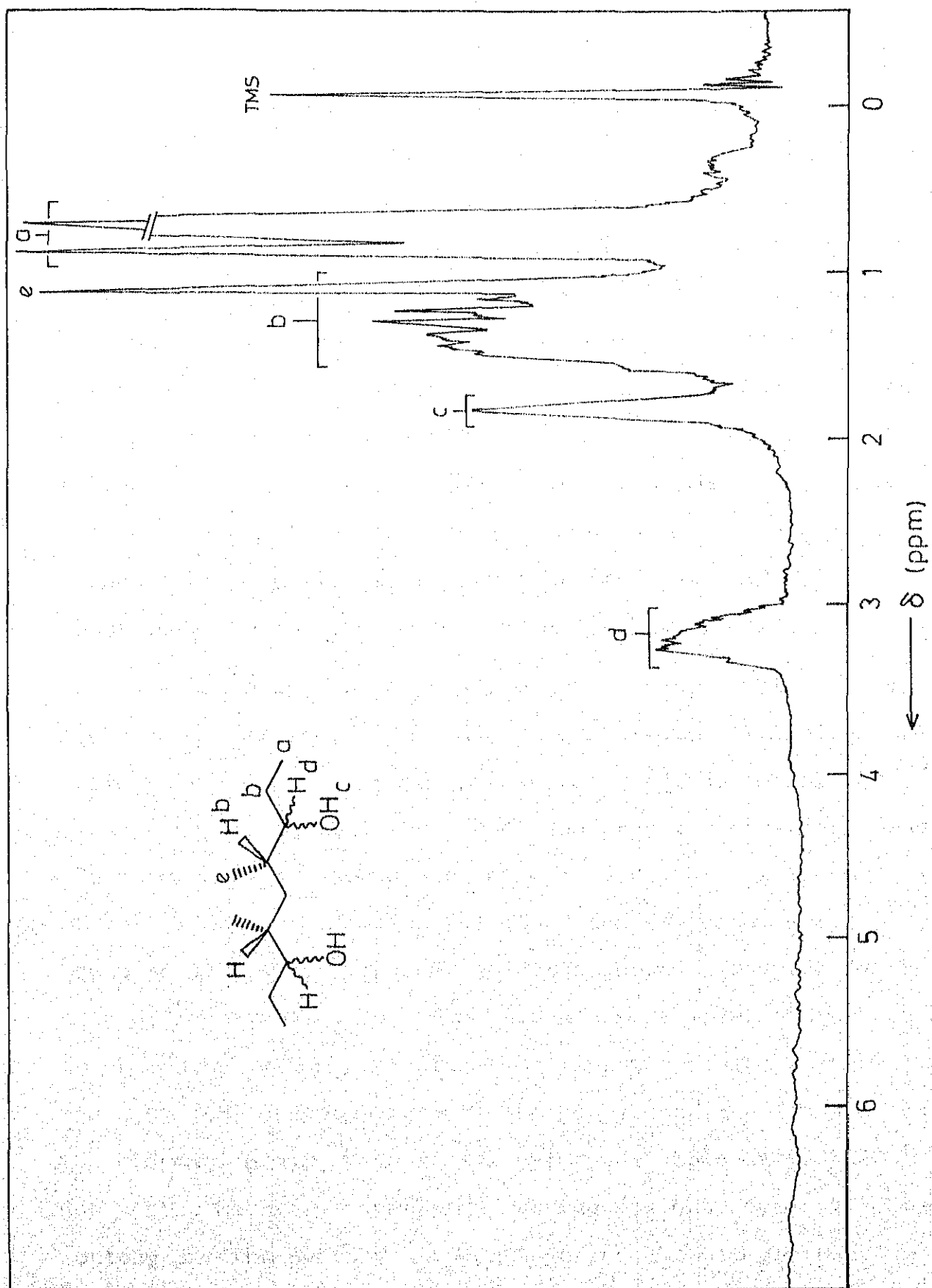


Fig. II-A-8 ^1H NMR spectrum (90 MHz) of 24.

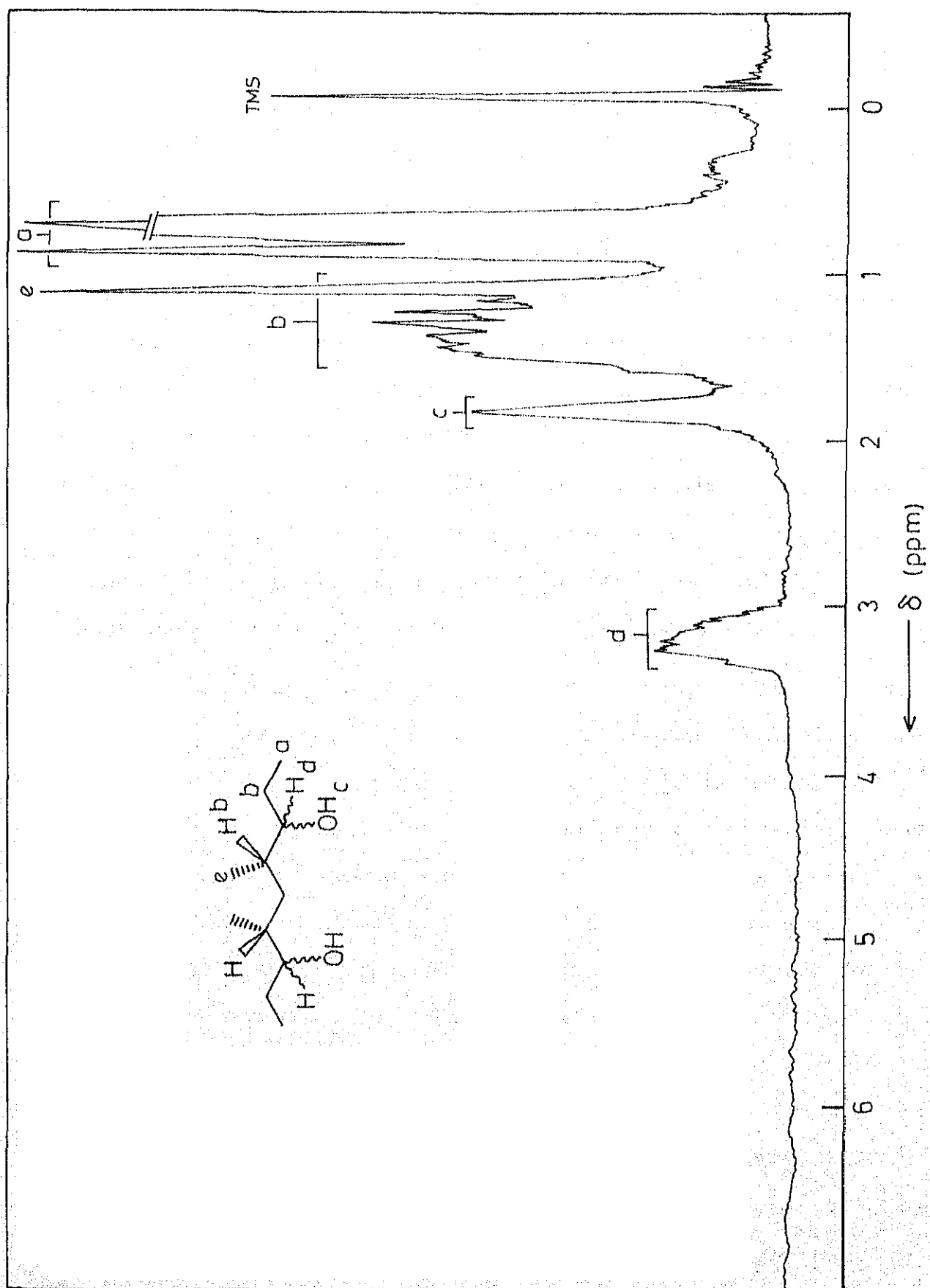


Fig. II-A-8 ¹H NMR spectrum (90 MHz) of 24.

The dihydroxy compound 24 was acetylated with two equivalents of acetic anhydride and 0.4 equivalents of dimethylaminopyridine in dichloromethane at room temperature. The diacetate 43 was obtained in quantitative yield (95%). The IR spectrum showed an absorption at 1730 cm^{-1} indicative of the ester group. The PMR spectrum showed a multiplet between $\delta 0.7$ and 1.1 (12H) assigned to the methyl group protons. The methylene and the methine protons showed a multiplet between 1.1 and 2.0 (8H). A singlet appeared at 2.03 (6H) assigned to the methyl group protons. The methine protons adjacent to the acetoxy group appeared as a multiplet at 4.72 (2H) (Fig. II.A.9). The mass spectrum indicated the molecular ion peak at m/e 272.

The dihydroxy compound 24, on treatment with 1.2 equivalents of acetic anhydride and 0.2 equivalents of dimethylaminopyridine yielded 63% of the monoacetate 42 and 10% of the diacetate 43 with 17% recovery of the starting material. The IR spectrum of 42 showed absorptions at 3360 and 1730 cm^{-1} characteristic of the hydroxyl group and the ester carbonyl group respectively. The PMR spectrum showed a doublet and a triplet superimposed, between $\delta 0.6$ and 1.06 (12H) corresponding to the methyl group protons. A multiplet appeared between 1.1 and 1.97 (8H) corresponding to the methylene, the methine and the hydroxyl group protons. A singlet was shown at 1.05 (3H) due to the methyl protons; the methine protons adjacent to the acetoxy and the hydroxyl groups appeared as multiplets at

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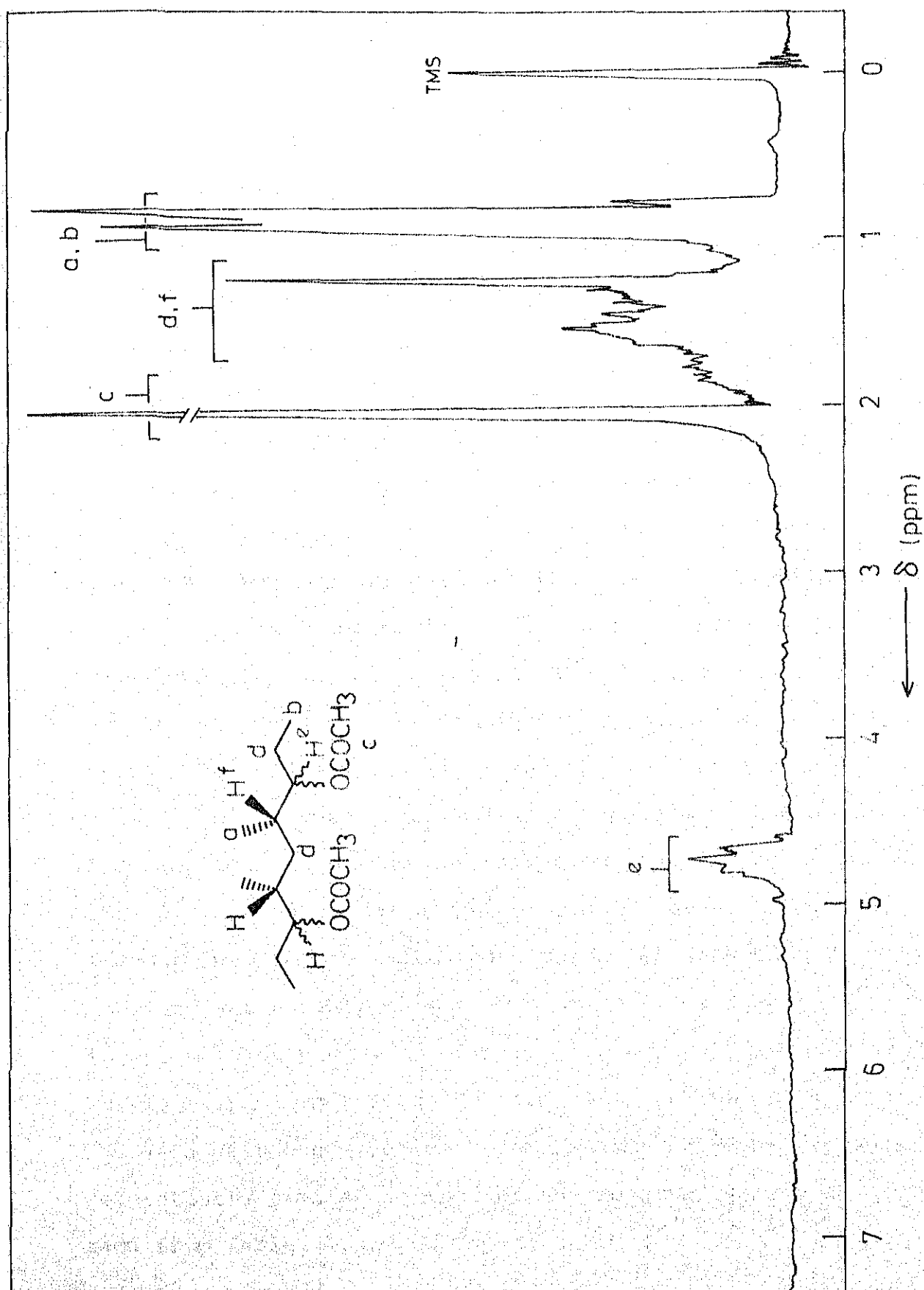


Fig. II-A-9 ^1H NMR spectrum (90 MHz) of 43.

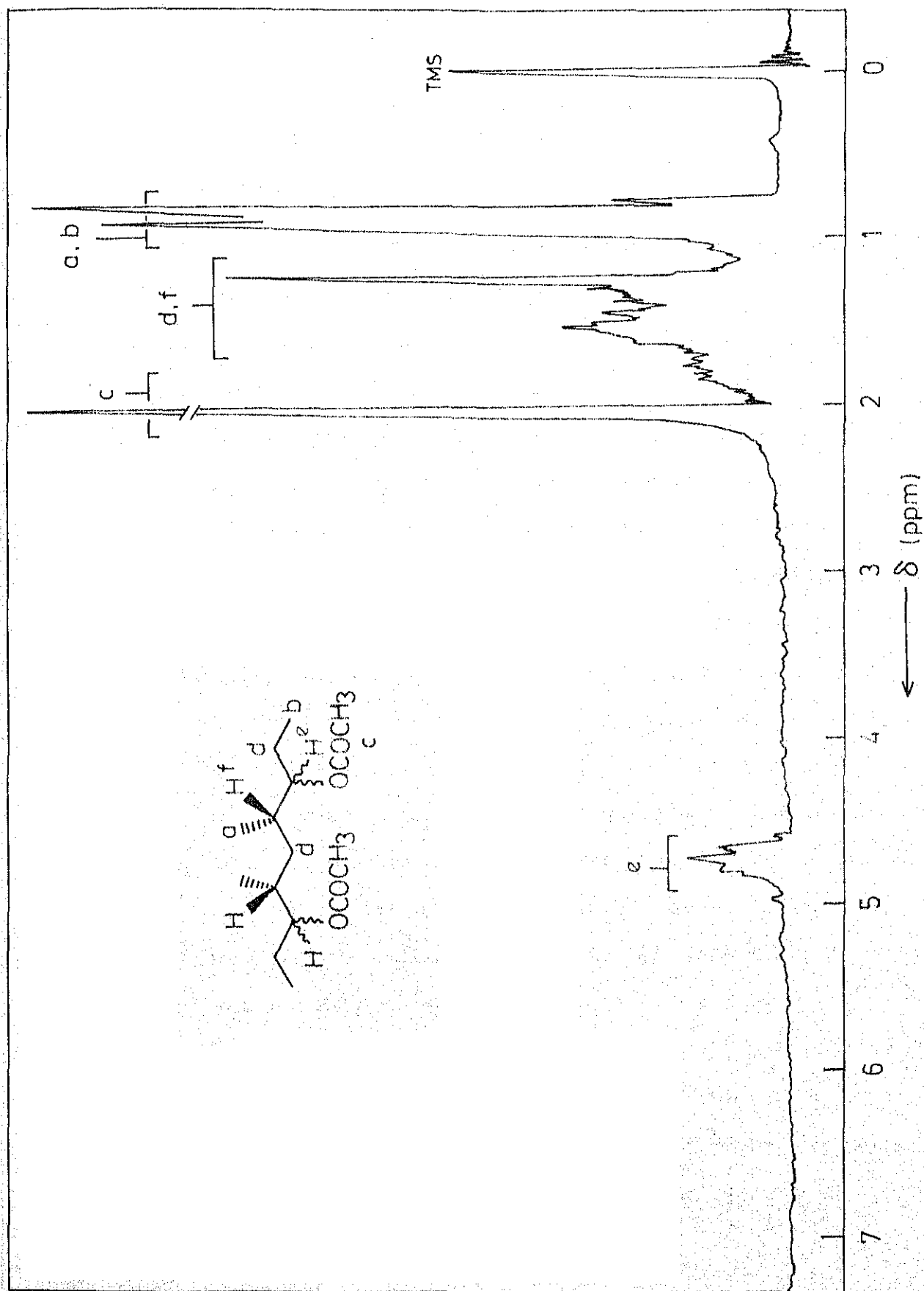


Fig. II-A-9 ^1H NMR spectrum (90 MHz) of 43.

3.36 (1H) and at 4.76 (1H) (Fig.II.A.10). The mass spectrum of 42 showed the molecular ion peak at m/e 230.

The oxidation of the hydroxyacetate 42 would lead to the acetate 2 of the pheromone. With a view to carrying out the oxidation under essentially neutral conditions to prevent the epimerization at C-4 of the product, the reaction was performed with Collins reagent³² in dichloromethane at 25°C to yield the ketoacetate 2 in 95% yield. The spectral data were closely similar to that reported for the acetate of the natural pheromone. The ketoacetate 2 showed two strong absorptions in the IR spectrum at 1730 and 1705 cm^{-1} characteristic of the ester and the keto functional groups. The PMR spectrum showed a triplet at 0.85 (6H, $J = 6$ Hz) corresponding to the methyl protons and a doublet at δ 1.03 (6H, $J = 7.5$ Hz) assigned to the methyl groups protons. A multiplet appeared between 1.16 and 1.96 (6H) due to the methylene protons and a singlet was traced at 2.0 (3H) due to the methyl group of acetate functionality. The methine protons indicated a multiplet between 2.2 and 2.8 (2H) and yet another multiplet centred at 4.6 (1H) was assigned to the methine proton adjacent to the acetoxy group (Fig.II.A.11). The mass spectrum showed the molecular ion peak at m/e 228. The CMR data of the synthetic pheromone (a mixture of stereoisomers) were closely similar to that of the reported values³ as could be seen from Table II.A.2.

3.36 (1H) and at 4.76 (1H) (Fig.II.A.10). The mass spectrum of 42 showed the molecular ion peak at m/e 230.

The oxidation of the hydroxyacetate 42 would lead to the acetate 2 of the pheromone. With a view to carrying out the oxidation under essentially neutral conditions to prevent the epimerization at C-4 of the product, the reaction was performed with Collins reagent³² in dichloromethane at 25°C to yield the ketoacetate 2 in 95% yield. The spectral data were closely similar to that reported for the acetate of the natural pheromone. The ketoacetate 2 showed two strong absorptions in the IR spectrum at 1730 and 1705 cm^{-1} characteristic of the ester and the keto functional groups. The PMR spectrum showed a triplet at 0.85 (6H, $J = 6$ Hz) corresponding to the methyl protons and a doublet at δ 1.03 (6H, $J = 7.5$ Hz) assigned to the methyl groups protons. A multiplet appeared between 1.16 and 1.96 (6H) due to the methylene protons and a singlet was traced at 2.0 (3H) due to the methyl group of acetate functionality. The methine protons indicated a multiplet between 2.2 and 2.8 (2H) and yet another multiplet centred at 4.6 (1H) was assigned to the methine proton adjacent to the acetoxy group (Fig.II.A.11). The mass spectrum showed the molecular ion peak at m/e 228. The CMR data of the synthetic pheromone (a mixture of stereoisomers) were closely similar to that of the reported values³ as could be seen from Table II.A.2.

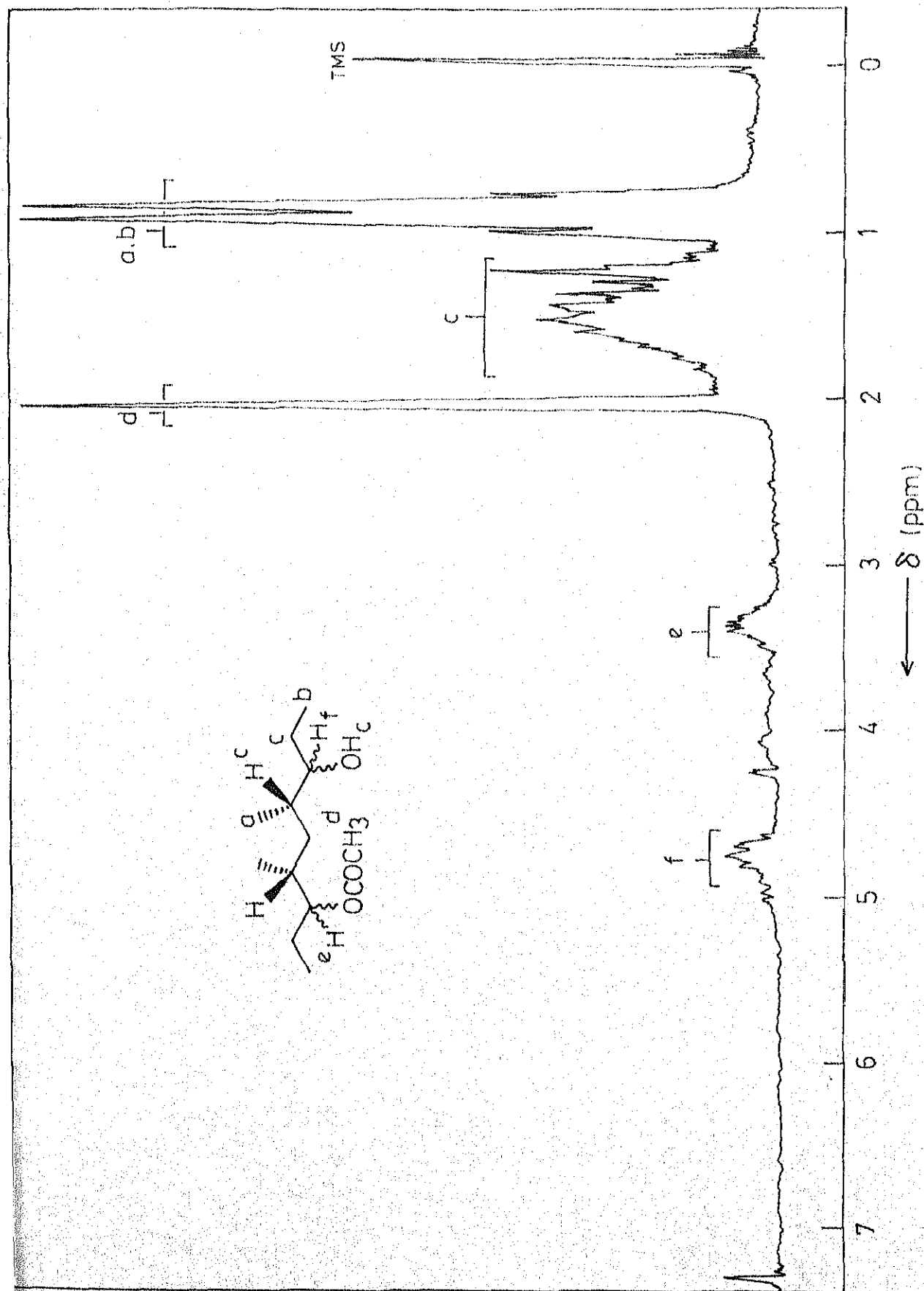


Fig. II-A-10 ^1H NMR spectrum (90 MHz) of 42.

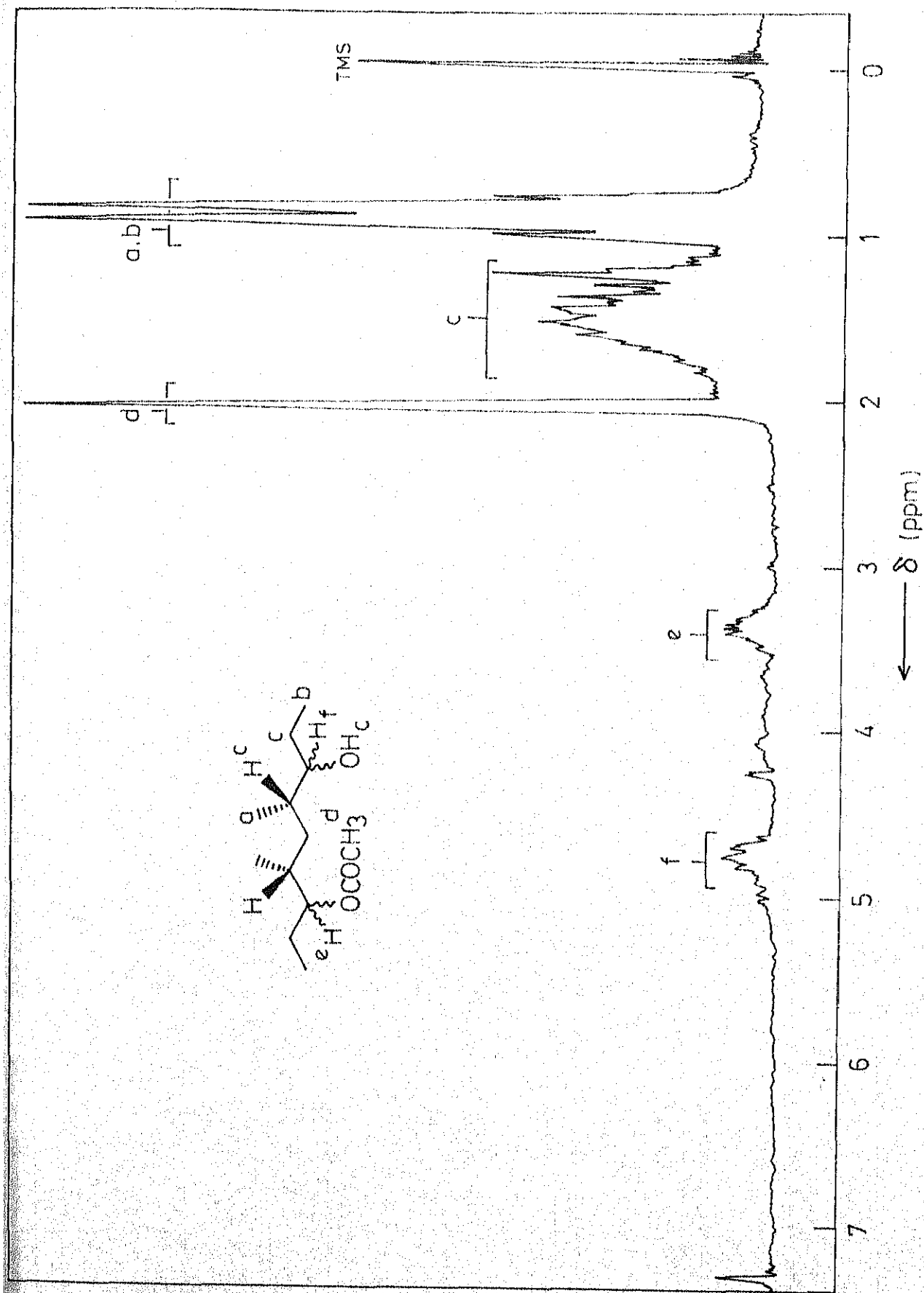


Fig. II A-10 ^1H NMR spectrum (90 MHz) of 42.

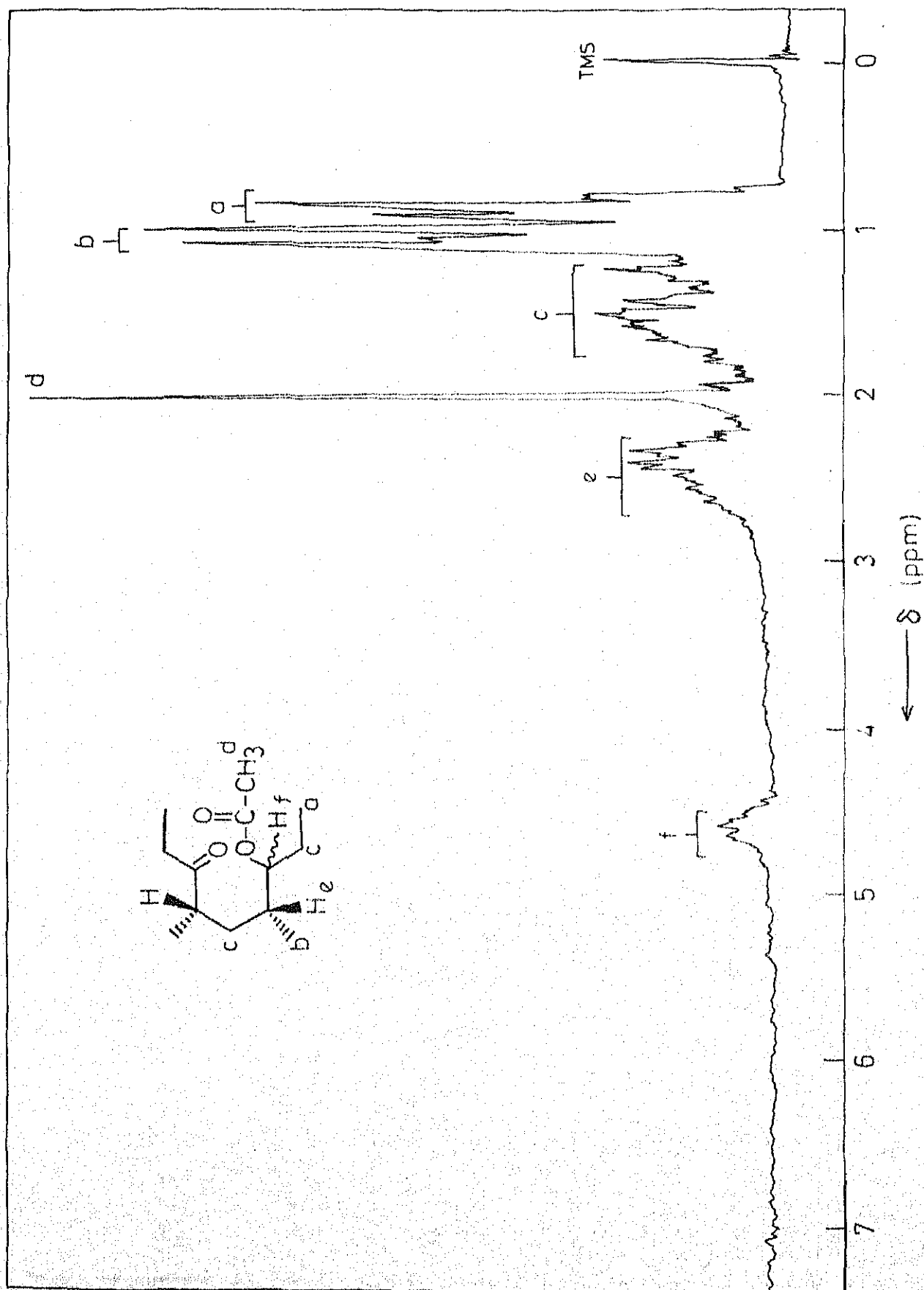
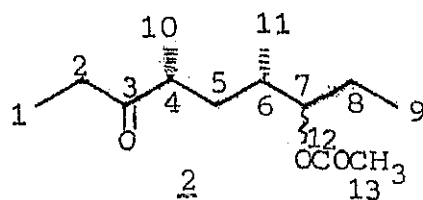


Fig. II-A.11 ¹H NMR spectrum (90 MHz) of **2**.

Table II.A.2 *CMR Spectral Data of the Acetate of the Sex Pheromone 2*



Carbon No.	Natural <u>2</u>	Synthetic <u>2</u>
1	7.84	7.84
2	34.22	34.29 34.38
3	214.88	214.71
4	43.53	43.59 44.08
5	24.22	23.56 24.36
6	33.70	33.88 34.13
7	78.04	77.32 78.06
8	35.98	35.78 36.61
9	10.18	9.98 10.11
10	16.67	17.30 17.98
11	14.45	14.73 15.98
12	170.88	171.00
13	21.06	21.02

II.A.4 EXPERIMENTAL

General Procedures

All reactions were performed in oven-dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified. Distilled water is used for aqueous work-ups. Reaction product solutions were concentrated using a Perfit rotary evaporator. Ozonation was carried out using Welsbach ozonator.

Materials

Commercial grade solvents were distilled prior to use. Petroleum ether used was the fraction 60-80°C. Diethyl ether and tetrahydrofuran were distilled from lithium aluminium hydride; acetone was distilled from potassium permanganate; triethyl amine and pyridine were distilled from potassium hydroxide pellets. Methylene chloride and chloroform were distilled from phosphorus pentoxide. tert-Butyl alcohol, ethyl alcohol, benzene and petroleum ether were distilled from sodium. Dimethyl sulphoxide was distilled from calcium hydride. Liquid ammonia was distilled from sodium.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60F-254 0.25 mm plates. Visualization of spots was effected by one or more of the

following techniques: (a) ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200°C; (d) immersion of the plate in a 3% solution of vanillin in ethanol containing 0.5% concentrated sulphuric acid, followed by heating to dry the plate, and then reimmersion and heating to ca. 200°.

Column chromatography was performed using 100-200 mesh Acme silica gel. The flash chromatography was performed using Acme thin-layer chromatography silica gel.

Physical Data

Melting points (m.p.) were determined with a Uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

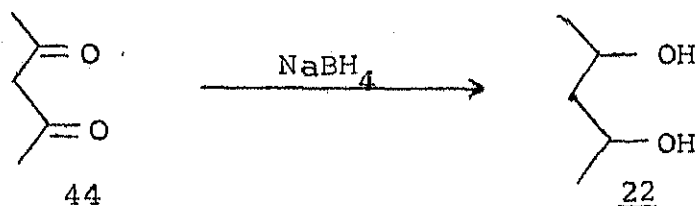
Infrared (IR) spectra were recorded on Perkin Elmer model 377 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 60 MHz on a Jeol PMX-60 instrument, at 80 MHz on a Bruker WP-80 instrument, at 90 MHz on a Varian EM-390 instrument and at 100 MHz on a Varian HA-100 and XL-100 instruments. Chemical shifts are reported in parts per million downfield from internal reference tetramethylsilane (δ). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet),

t (triplet), q (quartet), m (multiplet), etc. Coupling constants are reported wherever necessary and are expressed in Hz.

Mass spectra (MS) were measured on a VG Micromass 7070F mass spectrometer. Principal molecular fragments are reported.

II.A.4.1 Preparation of 2,4-Pentanediol (22)

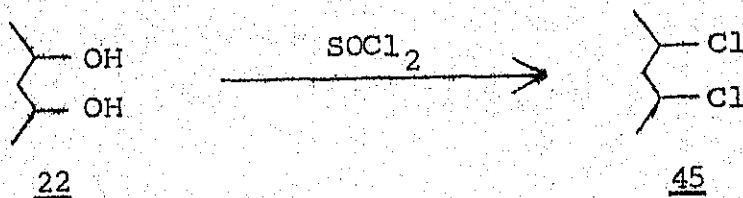


A solution of acetylacetone (28.5 g, 285 mmol) in methanol (85 mL) was added slowly to a stirred solution of sodium borohydride (7.14 g, 257 mmol) and sodium hydroxide (1.4 g) in water (71 mL), maintaining the temperature below -20°C . After the addition was complete, the solvents were removed under reduced pressure to leave a colourless solid. Glycerol (113 mL) was added and distilled to yield 23 g of 22 (77%), b.p. 86°C (6 mm) [lit.¹³ b.p. 98°C (10 mm)].

IR (CCl_4): $3385\ (\nu_{\text{O-H}})$.

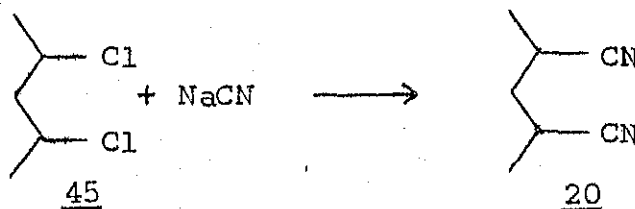
PMR (CDCl_3): 1.2 (d, 6H, $-\text{CH}_3$); 1.4 - 1.8 (m, 2H, $-\text{CH}_2$); 3.6 - 4.2 (m, 2H, $-\text{CH}$); 4.4 (s, 2H, $-\text{OH}$, D_2O exchangeable).

II.A.4.2 Preparation of 2,4-Dichloropentane (45)



To a mixture of 2,4-pentane diol (13.6 g, 131 mmol) and dry pyridine (1.58 ml) cooled at ca. 0°C, was added distilled thionyl chloride (61 g, 790 mmol). The mixture was refluxed for 3 h and poured slowly into crushed ice with stirring. Extracted the mixture with ether (4 x 60 mL). The ether layer was washed with 10% sodium bicarbonate solution (50 mL), followed by brine (50 mL) and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and fractionated to yield 14.6 g of 2,4-dichloropentane (80%), b.p. 46-48°C (20 mm) [lit.¹³ b.p. 40°C(12 mm)].

II.A.4.3 Preparation of 2,4-Dicyanopentane (20)



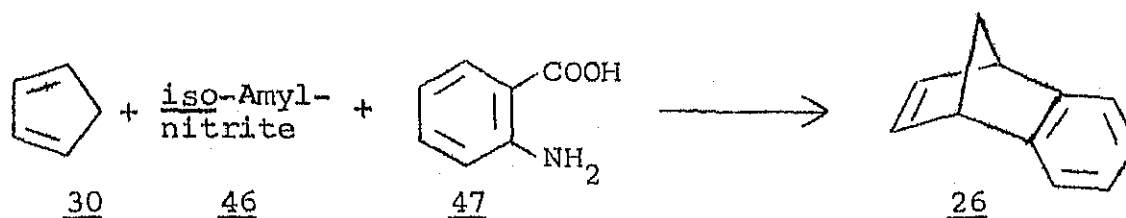
To a stirred slurry of sodium cyanide (8.32 g, 170 mmol) in dry dimethylsulfoxide (42 ml) at 120°C, 2,4-dichloropentane (10.0 g, 71 mmol) was added slowly over a period of 0.75 h. Refluxing was continued for 3 h; cooled and poured into a saturated solution of sodium chloride (50 ml). Enough water was added to dissolve the precipitated salt and extracted with chloroform (5 x 60 ml). The combined extract was washed with brine (2 x 50 ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and distilled to afford 6 g (70%) of the dicyanopentane, b.p. 125°C (10 mm)

[lit.¹² b.p. 94°C (2 mm)].

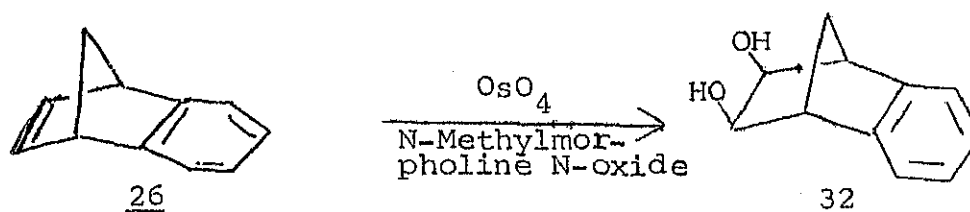
IR (CHCl₃): 2240 ($\nu_{\text{C}\equiv\text{N}}$).

PMR (CDCl₃): 1.3 (d, 6H, -CH₃); 1.8 - 2.0 (m, 2H, -CH₂);
2.6 - 3.0 (m, 2H, -CH).

II.A.4.4 Preparation of Benzonorbornadiene (26)



A solution of anthranilic acid (47, 68.5 g, 0.5 mol) and freshly distilled cyclopentadiene (33 g, 41 mL, 0.5 mol) in acetone (300 mL) was added over a period of 1.25 - 1.5 h to a refluxing, mechanically stirred solution of iso-amyl nitrite (65 g, 74 mL, 0.55 mol) in dichloromethane (700 mL), in a two litre 3-necked flask. After the addition was completed, the dark reaction mixture was refluxed for 0.5 h. It was then cooled and made basic with 10% aqueous potassium hydroxide solution (100 mL) and the solvents were removed. The residual black oil was steam distilled and the distillate was collected (ca. 300 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 100 mL). The ether extract was dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residual yellow oil was fractionated to give 40 g of benzonorbornadiene 29, b.p. 80-82°C (20 mm) [lit.¹⁵ b.p. 78-79°C (20 mm)].

II.A.4.5 Preparation of Diol 32

A solution of 26 (5.68 g, 40 mmol) and N-methylmorpholine-N-oxide (7.95 g, 52 mmol) in acetone (150 mL) and distilled water (60 mL) was treated with a solution of osmium tetroxide (0.1 g in 5 mL of THF, 0.4 mmol) and the resulting mixture was stirred for 24 h. Ethyl acetate (50 mL) and saturated sodium bisulphite solution (40 mL) were added and the resulting two-phase mixture was stirred vigorously for 0.25 h. The organic layer was separated and the aqueous phase was then extracted with ethyl acetate. The combined organic layer was washed with saturated sodium chloride solution; dried over anhydrous sodium sulphate; filtered and concentrated to afford 6.5 g (93%) of a crystalline solid (recrystallised from ethyl-acetate-hexane, 80:20), m.p. 168-169°C.

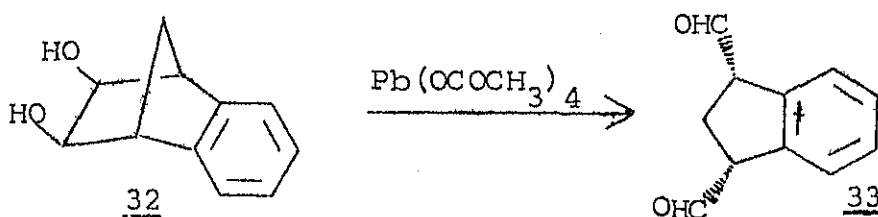
IR (KBr): 3400, 3250 ($\nu_{\text{O-H}}$).

PMR (CDCl_3): 2.06 (q, 2H, $-\text{CH}_2$, $J = 9$ Hz); 3.17 (s, 2H, $-\text{CH}$); 3.69 (s, 2H, $-\text{CH}$); 4.86 (s, 2H, $-\text{OH}$, D_2O exchangeable); 7.08 (s, slightly split, 4H, aromatic).

MS (m/e): 176 (M^+), 158, 145, 129, 128, 116, 115, 91, 77.

Anal. for $\text{C}_{11}\text{H}_{12}\text{O}_2$: Calcd: C, 75.00; H, 6.82.

Found: C, 75.20; H, 6.90.

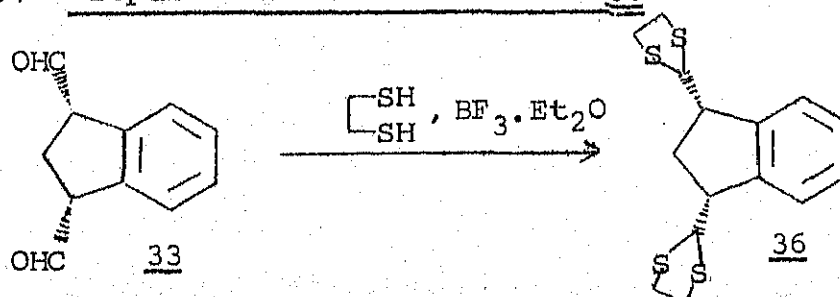
II.A.4.6 Preparation of Dialdehyde 33

To a solution of diol 32 (4.0 g, 22.7 mmol) in distilled benzene (40 mL) at room temperature, was added lead tetraacetate (11.89 g, 26.9 mmol) in portions. The resulting mixture was stirred at room temperature for 5 minutes. Diluted the reaction mixture with anhydrous ether and filtered through celite and anhydrous magnesium sulphate. Concentration of the filtrate afforded 3.75 g (95%) of the dialdehyde 33 as a pale yellow oil.

IR (thin film): 1720 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 2.33 - 3.13 (m, 2H, CH_2); 4.06 (m, 2H, CH); 7.36 (s, 4H, aromatic); 9.66 (d, 2H, aldehydic, $J = 3$ Hz).

MS (m/e): 174 (M^+), 146, 131, 118, 117, 115, 91, 77.

II.A.4.7 Preparation of Dithioacetal 36

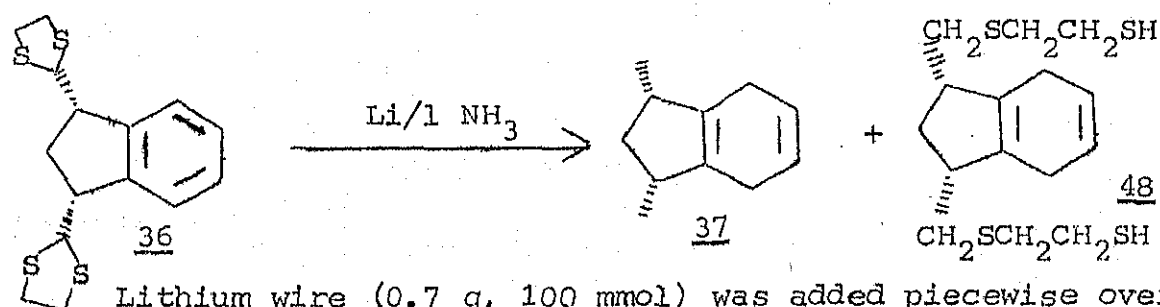
A solution of the dialdehyde 33 (0.87g, 5 mmol) in dichloromethane (15 mL) was treated with distilled 1,2-ethanedithiol (0.958 g, 10.2 mmol) and distilled boron trifluoride etherate (1.42 g, 1.23 mL, 10 mmol) and the resulting solution was

stirred at room temperature for 2 h. The reaction mixture was diluted with ether and extracted with half-saturated sodium bicarbonate solution (10 mL) and saturated sodium chloride solution (20 mL); dried over anhydrous magnesium sulphate, filtered, and concentrated to afford 1.37 g (84%) of 36 as a colourless oil, which was used in the next step without purification.

PMR (CDCl_3): 1.84 - 2.82 (m, 2H, $-\text{CH}_2-$); 3.06 - 3.66 (m, 10 H, $-\text{CH}_2-$, $-\text{CH}-$); 5.02 (d, 2H, $-\text{CH}-$, $J = 7$ Hz); 7.0 - 7.6 (m, 4H, aromatic).

MS (m/e): 326 (M^+), 221, 187, 171, 149, 128, 105, 84, 77, 61.

II.A.4.8 Metal-Ammonia Reduction of 36



Lithium wire (0.7 g, 100 mmol) was added piecewise over 0.5 h to liquid ammonia (50 mL) at reflux. To the resulting blue solution, a solution of dithioacetal 36 (1.3 g, 3.9 mmol) in tetrahydrofuran (15 mL) and distilled tert-butanol (3.7 mL, 50 mmol) was slowly added over 0.5 h. The reaction mixture was refluxed for additional 4 h. Ammonium chloride (10 g) was added in portions and ammonia was allowed to evaporate over

ca. 12 h. The solid residue was dissolved in water (50 mL) and extracted with ether (4 x 50 mL). The combined organic phase was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated to yield a yellow oil. The crude product was purified by flash column chromatography (elution with petroleum ether) to obtain 0.285 g of dihydrodimethylindane (37, 50%) and 0.52 g of product 48 resulting from partial hydrogenolysis.

Diene 37

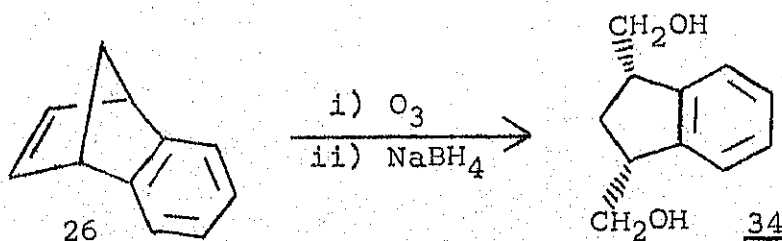
PMR (CDCl_3): 1.3 (d, 6H, $-\text{CH}_3$, $J = 7$ Hz); 2.46 (m, 2H, $-\overset{|}{\text{CH}}_2$); 3.1 (m, 2H, $-\overset{|}{\text{CH}}$); 7.15 (s, 4H, aromatic).

Compound 48

PMR (CDCl_3): 1.2 - 2.2 (m, 2H, $-\overset{|}{\text{CH}}_2$), 2.2 - 3.6 (m, 18H, $-\overset{|}{\text{CH}}_2$, $-\overset{|}{\text{CH}}$); 4.06 (s, 2H, $-\text{SH}$), 5.68 (m, 2H, vinylic).

MS (m/e): 332 (M^+), 238, 225, 189, 161, 143, 131, 117, 91, 61.

II.A.4.9 Preparation of Dihydroxy Compound 34



Ozone gas was bubbled through a solution of benzonorbornadiene 26 (14.2 g, 100 mmol) dissolved in dry dichloromethane

(200 mL) at ca. -78°C . The reaction was followed by the disappearance of the starting material through tlc analysis. A solution of sodium borohydride (30.4 g, 800 mmol) dissolved in cold 50% aqueous ethanol (200 mL) was added slowly to the stirred ozonide mixture, while the temperature is maintained at ca. 25°C by occasional ice bath cooling. The reaction mixture was warmed up in a water bath for 2 h with stirring and allowed to stand overnight at room temperature. The mixture was acidified with acetic acid and extracted with ethyl acetate (4 x 200 mL). The organic extract was washed with sodium bicarbonate solution (100 mL) followed by brine (100 mL) and dried over anhydrous magnesium sulphate. The solution was filtered and concentrated to afford a thick oil which was crystallised with ethyl acetate-hexane (1:1), to furnish 12.7 g (70%) of a white solid, m.p. $99-100^{\circ}\text{C}$. From two such ozonations, 25 g of the diol 34 was obtained.

IR (KBr): 3290 ($\nu_{\text{O-H}}$).

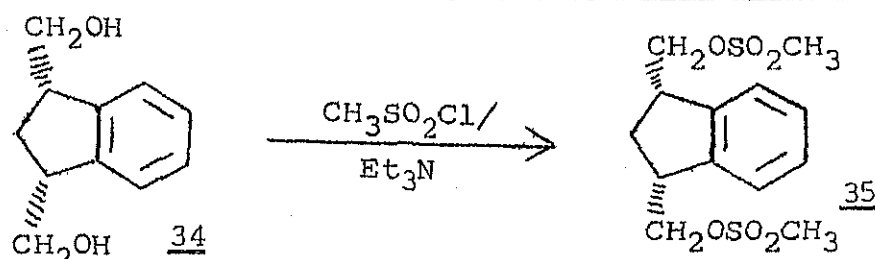
PMR (CDCl_3): 1.64-2.72 (m, 2H, $-\overset{|}{\text{CH}}_2$); 2.18 (s, 2H, $-\text{OH}$); 3.44 (m, 2H, $-\overset{|}{\text{CH}}$); 3.92 (d, 4H, $-\overset{|}{\text{CH}}_2$); 7.3 (s, 4H, aromatic).

MS (m/e): 178 (M^+), 161, 148, 130, 129, 117, 103, 91, 77.

Anal. for $\text{C}_{11}\text{H}_{14}\text{O}_2$: Calcd. C, 74.15; H, 7.86.

Found C, 74.30, H, 7.70.

II.A.4.10 Preparation of Dimesylate 35 (X = OMs)

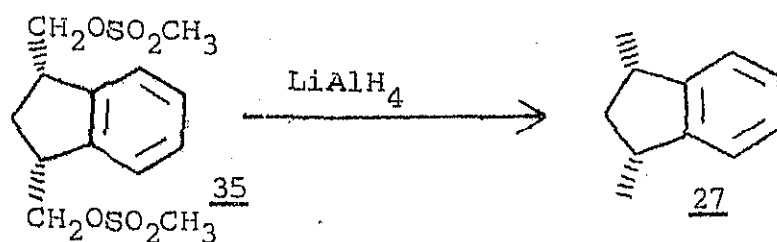


To a solution of 34 (5.34 g, 30 mmol) and triethylamine (6.6 g, 66 mmol) in dry dichloromethane (70 mL) was added slowly methanesulphonyl chloride (6.84 g, 60 mmol) dropwise over 0.5 h at ca. -20°C . The resulting mixture was stirred for 6 h at -20°C . The reaction mixture was transferred to a separatory funnel with the aid of more dichloromethane and was first washed with ice water (50 mL), followed by cold 10% hydrochloric acid (50 mL), saturated sodium bicarbonate solution (50 mL) and brine (50 mL). The organic extract was dried over anhydrous sodium sulphate, followed by evaporation of solvent under reduced pressure, affording 9.5 g of dimesylate 35 (95%) which was recrystallised from dichloromethane-hexane (1:1), m.p. $134\text{--}135^{\circ}\text{C}$. From four such reactions, 37.0 g of the dimesylate was obtained.

IR (KBr): 1350, 1350(d), 1170, 1160(d) ($\nu_{-\text{SO}_2-}$).

PMR (CDCl_3): 1.5 – 2.5 (m, 2H, $-\overset{|}{\text{CH}}_2$); 3.0 (s, 6H, $-\text{CH}_3$); 6.65 (m, 2H, $-\overset{|}{\text{CH}}$); 4.4 (m, 4H, $-\overset{|}{\text{CH}}_2$); 7.34 (s, 4H, aromatic).

MS (m/e): 238 ($\text{M}^+ - \text{CH}_3\text{SO}_2\text{OH}$), 142, 129, 115, 102, 91, 79, 63.

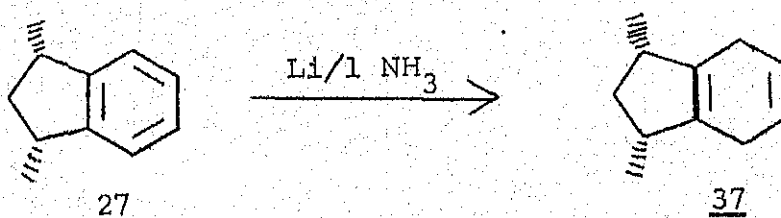
II.A.4.11 Preparation of Dimethylindane (27)

To a slurry of lithium aluminium hydride (8.2 g, 216 mmol) in absolute ether (250 mL) was added with efficient stirring dimesylate 35 in several portions (9.02 g, 27 mmol). The resulting mixture was refluxed for 2 h, cooled and water was added slowly (8.2 mL), followed by 10% aqueous sodium hydroxide solution (8.2 mL) and then again water (16.4 mL). The precipitated hydroxides were filtered through anhydrous magnesium sulphate and the filter cake was washed with ether (200 mL). The filtrate was evaporated to afford 3.15 g (80%) of a liquid.

The crude product from four such reactions yielded 12.0 g of the hydrocarbon 27, b.p. 80-82°C (7 mm), [lit.¹⁷ b.p. 202.3°C (740.5 mm)].

PMR (CDCl_3): 1.3 (d, 6H, $-\text{CH}_3$, $J = 7$ Hz); 2.46 (m, 2H, $-\text{CH}_2$); 3.1 (m, 2H, $-\text{CH}$); 7.15 (s, 4H, aromatic).

MS (m/e): 145 (M^+), 131, 115, 91, 77.

II.A.4.12 Preparation of Diene 37

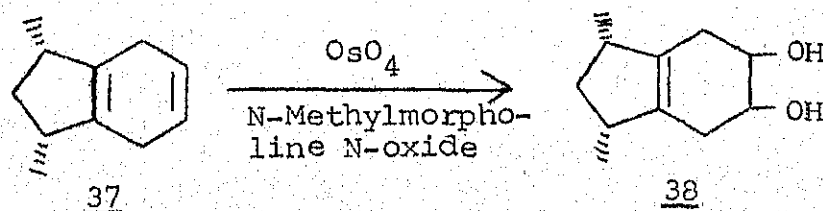
Lithium (4.8 g, 700 mmol) pieces were added slowly to refluxing liquid ammonia (400 mL) over 0.25 h. To the resulting blue solution, 27 (10.22 g, 70 mmol) was added in anhydrous tetrahydrofuran (60 mL) and absolute ethanol (24 mL) slowly in about 0.3 h. The reaction mixture was mechanically stirred under reflux for 3 h. Solid ammonium chloride was added to destroy the excess lithium and the reaction mixture was left overnight to allow the ammonia to evaporate. Water (100 mL) was added to the curdy mass and extracted with ether (4 x 100 mL). The ether extract was washed with water (2 x 100 mL) followed by brine (100 mL) and dried over anhydrous sodium sulphate. Filtered and concentrated the extract to afford 9.8 g (95%) of an oil which was fractionated, b.p. 62-64°C (7 mm).

IR (thin film): 1650 ($\nu_{C=C}$).

PMR ($CDCl_3$): 1.0 (d, 6H, $-CH_3$, $J=6$ Hz); 2.16 - 2.9 (m, 8H, $-CH_2-$, $-\dot{C}H-$); 5.74 (s, 2H, vinylic).

MS (m/e): 148 (M^+), 133, 132, 119, 118, 115, 107, 105, 93, 91, 77, 73, 65, 55.

II.A.4.13 Preparation of Diol 38



A solution of 37 (0.74 g, 5 mmol) and N-methylmorpholine-N-oxide (0.995 g, 6.5 mmol) in acetone (25 mL) and distilled water (10 mL) was treated with a solution of osmium tetroxide (0.127 g in 6 mL of tetrahydrofuran, 0.5 mmol) and the resulting mixture was stirred at room temperature for 80 h. Ethyl acetate (50 mL) and saturated sodium bisulphite solution (5 mL) were added and the two-phase mixture was stirred vigorously for 0.25 h. The organic layer was removed and the aqueous phase was extracted with ethyl acetate (4 x 40 mL); the combined organic layer was washed with saturated sodium chloride solution (50 mL), dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford a green viscous liquid. The crude product from twelve such small-scale reactions was subjected to flash chromatography to yield 5.4 g (61%) of the unchanged starting material 37 (elution with petroleum ether) and 2.7 g (25%) of the diol 38 (elution with 4:1, ether-petroleum ether). The product 38 obtained by column chromatography was recrystallised from ether-petroleum ether (3:2), m.p. 99-100°C.

IR (KBr): 3330 ($\nu_{\text{O-H}}$).

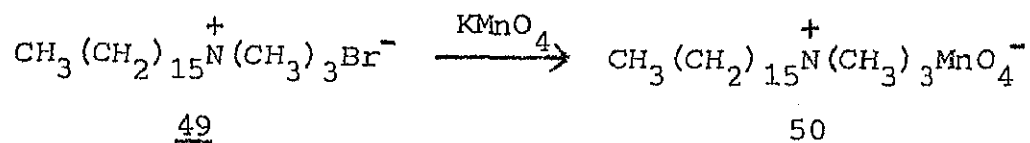
PMR (CDCl_3): 0.98 (d, 6H, $-\text{CH}_3$, $J = 6 \text{ Hz}$); 1.8 - 2.7 (m, 8H, $-\text{CH}_2$, $-\text{CH}$, $-\text{OH}$); 3.96 (m, 2H, $-\text{CH}$).

MS (m/e): 182 (M^+), 164, 149, 147, 131, 121, 120, 107, 105, 93, 91.

Anal. for $\text{C}_{11}\text{H}_{18}\text{O}_2$: Calcd. C, 72.52; H, 9.89.

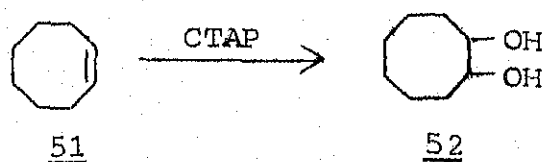
Found C, 72.65; H, 9.92.

II.A.4.14 Preparation of Cetyltrimethylammonium permanganate (50, CTAP)



To a stirred solution of potassium permanganate (3.168 g, 20 mmol) in water (100 mL) at ca. 20°C, was added slowly an aqueous saturated solution of cetyltrimethylammonium bromide 49 (8.02 g, 22 mmol) over 20 minutes. A fine violet coloured precipitate was formed immediately. The viscous mixture was stirred for an additional 0.5 h and filtered. The precipitate was washed thoroughly with water and dried in a desiccator over phosphorus pentoxide in vacuo for 3 h which was stored in a brown bottle in the refrigerator. The compound 50 decomposed at 85°C.

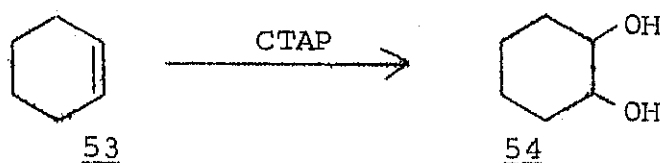
II.A.4.15a Oxidation of Cyclooctene (51)



To a solution of 51 (0.22 g, 2 mmol) in tert-butanol (1 mL) was added slowly a solution of CTAP (0.807 g, 2 mmol) in tert-butanol (8 mL) and water (3 mL) at ca. 20°C. The resulting mixture was stirred for 1 h. Chloroform (20 mL) and 5% aqueous sodium hydroxide (5 mL) were added, stirred for 0.5 h and the organic layer was separated. The aqueous phase

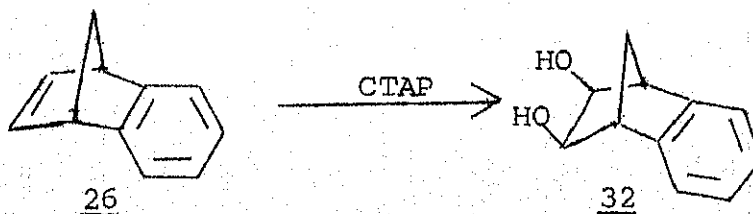
was extracted with chloroform (3 x 20 mL), washed with brine and dried over anhydrous magnesium sulphate. Filtered and evaporated the chloroform under reduced pressure to afford 0.21 g of the diol 52 (73%), m.p. 78-79°C (lit.²⁷ m.p. 78-79°C).

II.A.4.15b Oxidation of Cyclohexene (53)



The reaction was performed as above with 53 (0.082 g, 1 mmol) and CTAP (0.403 g, 1 mmol) in dichloromethane (12 mL) for 1 h. The dichloromethane was evaporated to half the volume under reduced pressure and the reaction mixture was diluted with ether and filtered through a pad of celite and anhydrous magnesium sulphate. Washed the celite a few times with chloroform (3 x 10 mL). The filtrate was evaporated under reduced pressure to afford 0.1 g (86%) of the diol 54, m.p. 97-98°C (lit.²⁸ m.p. 97-98°C).

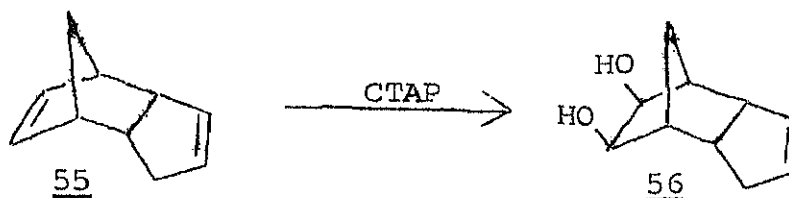
II.A.4.15c Oxidation of Benzonorbornadiene (26)



The reaction was carried out with 26 (0.071 g, 0.5 mmol) and CTAP (0.201 g, 0.5 mmol) as above, in dichloromethane (10 mL)

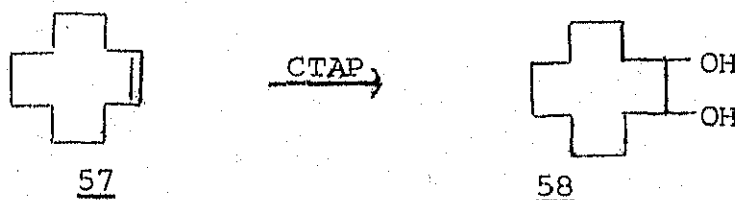
for 3 h, to yield 0.065 g (73%) of the diol 32, m.p. 168-169°C.

II.A.4.15d Oxidation of *endo*-Dicyclopentadiene (55)

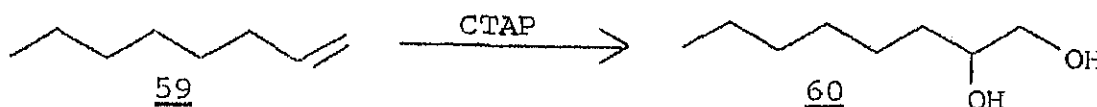


The reaction was carried out with 55 (0.065 g, 0.5 mmol) under identical conditions as above with CTAP (0.201 g, 0.5 mmol) for 4 h to afford a mixture. The crude product was purified by column chromatography over silica gel, to yield 0.11 g of the unreacted starting material (elution with petroleum ether) and 0.11 g (86%) of the pure diol 56, m.p. 48-49°C (lit.¹⁹ m.p. 48-51°C).

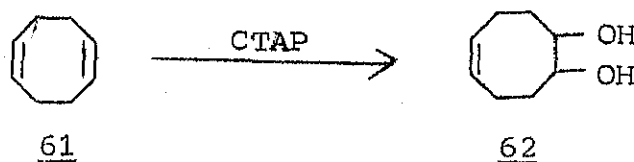
II.A.4.15e Oxidation of Cyclododecene (57)



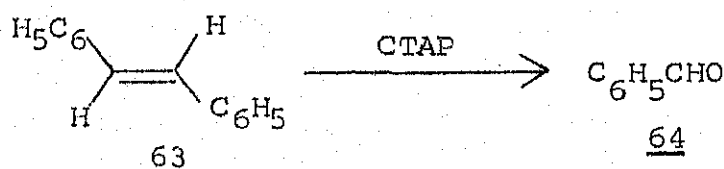
The reaction was performed under identical conditions as above with 57 (0.166 g, 1 mmol) and CTAP (0.403 g, 1 mmol) for 5 h in dichloromethane to yield a mixture of compounds. The crude mixture was chromatographed over silica gel to yield 0.04 g of the unchanged olefin 57 (elution with petroleum ether) and 0.097 g of the diol 58 (65%) (elution with 1:1 ether-petroleum ether), m.p. 157-157.5°C (lit.²⁹ m.p. 157-158°C).

II.A.4.15f Oxidation of 1-Octene (59)

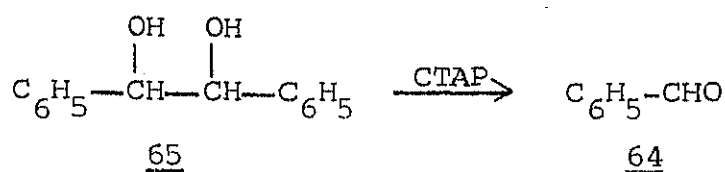
The reaction was carried out under analogous conditions with 59 (0.056 g, 0.5 mmol) and CTAP (0.201 g, 0.5 mmol) for 2 h, to yield 0.062 g of the diol 61 (85%), which was compared with the authentic sample.¹⁹

II.A.4.15g Oxidation of 1,5-Cyclooctadiene (61)

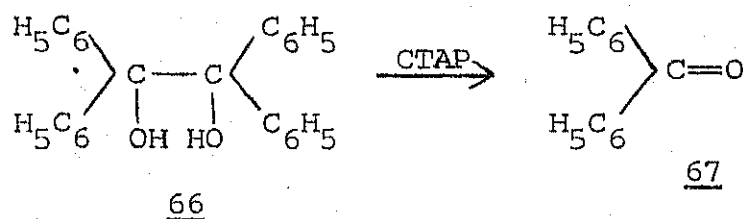
The reaction was carried out as earlier with 61 (0.108 g, 1 mmol) and CTAP (0.403 g, 1 mmol) for 1 h to yield 0.049 g of diol 63 (35%) m.p. 105-106°C (lit.³¹ m.p. 105-106°C).

II.A.4.15h Oxidation of *trans*-Stilbene (63)

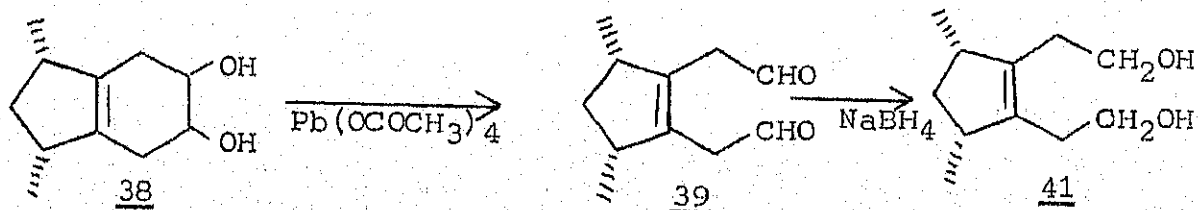
The reaction performed under similar conditions as above with 63 (0.18 g, 1 mmol) and CTAP (0.403 g, 1 mmol) in dichloromethane for 1 h, yielded 0.09 g of the unchanged 63 and 0.047 g (90%) of benzaldehyde (64).

II.A.4.15i Oxidation of Hydroxybenzoin (65)

The reaction was carried out with 65 (0.107 g, 0.5 mmol) and CTAP (0.201 g, 0.5 mmol) for 0.5 h under analogous conditions to yield 0.103 g (97%) of 64.

II.A.4.15j Oxidation of Benzopinacol (66)

The reaction was performed under identical conditions with 66 (0.184 g, 0.5 mmol) and CTAP (0.201 g, 0.5 mmol) for 0.5 h to yield 0.103 g (89%) of benzophenone (67) m.p. 47°C (mixture m.p. 47-48°C).

II.A.4.16 Preparation of Diol 41

To a solution of the diol 38 (2.18 g, 12 mmol) in dry benzene (20 mL) was added lead tetraacetate (6.4 g, 14.4 mmol)

in portions and the resulting mixture was stirred at room temperature for 0.3 h. The reaction mixture was diluted with anhydrous ether (50 mL) and filtered through a pad of celite and anhydrous magnesium sulphate. The filtrate upon concentration afforded 1.94 g of a pale yellow oil which was immediately used in the next step.

The crude product from the above reaction was dissolved in ethanol (20 mL) and sodium borohydride (1.368 g, 36 mmol) was added at 0°C. The resulting mixture was stirred for 3 h at 0°C. Crushed ice was added and the reaction mixture was allowed to warm up to room temperature and extracted with chloroform (4 x 50 mL). Washed the organic layer with brine and dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to yield a colourless oil, which was crystallised (4:1 ether-petroleum ether) to afford 1.87 g of a solid, m.p. 59-60°C (overall yield of 85%, from diol 38).

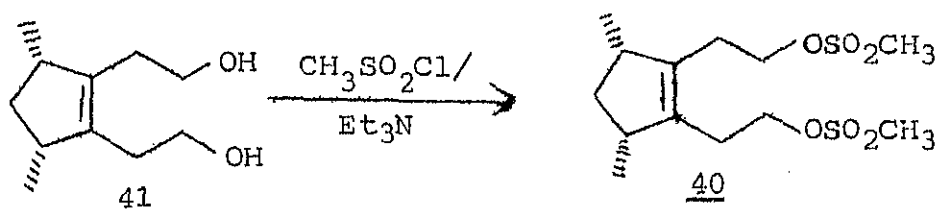
IR (CHCl₃): 3350 ($\nu_{\text{O-H}}$).

PMR (CDCl₃): 1.0 (d, 6H, -CH₃, J = 7 Hz); 2.04 - 2.8 (m, 8H, -CH₂, -CH); 3.02 (br, 2H, -OH, D₂O exchangeable); 3.54 - 3.8 (m, 4H, -CH₂).

MS (m/e): 184 (M⁺), 166, 151, 139, 137, 135, 133, 121, 120, 109, 107, 105, 95, 93, 91, 81, 79, 77.

Anal. for C₁₁H₂₀O₂: Calcd. C, 71.73; H, 10.86.

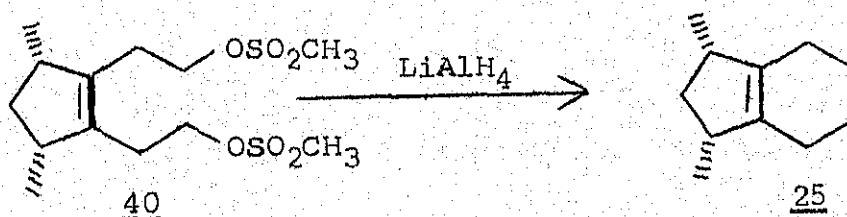
Found C, 71.68; H, 10.70.

II.A.4.17 Preparation of Dimesylate 40

To a solution of 41 (1.8 g, 9.78 mmol) and triethylamine (2.17 g, 21.52 mmol) in tetrahydrofuran (20 mL) maintained at -20°C , was added slowly methanesulphonyl chloride (2.22 g, 19.56 mmol) over 0.25 h. The resulting solution was stirred at -20°C for an additional 2 h. The mixture was then transferred to a separatory funnel by means of dichloromethane; washed successively with cold water (2 x 20 mL), cold 10% hydrochloric acid (20 mL), cold saturated sodium bicarbonate solution (20 mL) and then with brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give a yellow liquid which was filtered through a short silica gel pad to yield 3.03 g (91%) of dimesylate 40 (elution with 1:1 ether-petroleum ether).

IR (CHCl_3): 1170 (d, $\nu_{-\text{SO}_2-}$).

PMR (CDCl_3): 1.03 (d, 6H, $-\text{CH}_3$, $J = 6$ Hz); 2.06 - 2.83 (m, 8H, $-\text{CH}_2$, $-\text{CH}$); 2.96 (s, 6H, $-\text{CH}_3$); 4.16 (m, 4H, $-\text{CH}_2$).

II.A.4.18 Preparation of Hydrocarbon 25

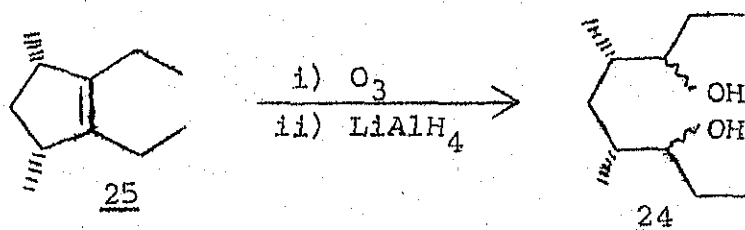
To a slurry of lithium aluminium hydride (2.58 g, 68 mmol) in anhydrous ether (100 mL) was added the dimesylate 40 (2.89 g, 8.5 mmol) in ether (20 mL) slowly and refluxed the resulting mixture for 2 h. Moist sodium sulphate was added slowly until no more gas evolution was seen. Filtered the reaction mixture and washed the residue with ether several times. Evaporated the filtrate to afford an oil which was purified by flash column chromatography to yield 0.775 g of the hydrocarbon 25 (60%).

IR (CHCl_3): 1620 ($\nu_{\text{C}=\text{C}}$).

PMR (CCl_4): 0.91 (t, 6H, $-\text{CH}_3$, $J = 7$ Hz); 0.98 (d, 6H, $-\text{CH}_3$, $J = 7.5$ Hz); 1.82 - 2.38 (m, 6H, $-\text{CH}_2-$); 2.58 (q, 2H, $-\text{CH}-$, $J = 7$ Hz).

MS (m/e): 152 (M^+), 137, 123, 121, 119, 109, 107, 105, 96, 92, 82.

II.A.4.19 Preparation of Dihydroxy Compound 24



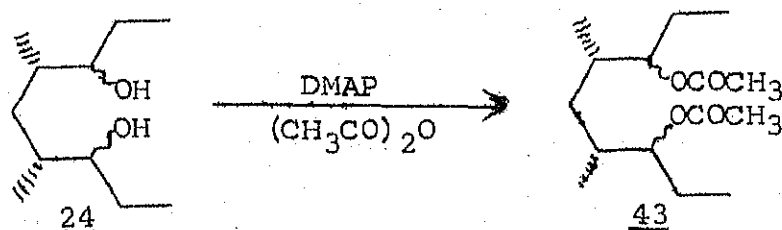
Ozone was bubbled through a solution of 25 (0.684 g, 4.5 mmol) in dichloromethane (15 mL) maintained at 0°C. When the thin layer chromatography showed the disappearance of starting material, the dichloromethane was evaporated under reduced pressure. The ozonide was dissolved in tetrahydrofuran (15 mL) and lithium aluminium hydride (1.368 g, 36 mmol) was added in

portions. The resulting mixture was stirred at room temperature for 2 h. Moist sodium sulphate was added to the cooled reaction mixture and filtered. The filter cake was washed several times with ether and the filtrate was evaporated to yield an oil which was purified by flash chromatography to afford 0.778 g (92%) of the dihydroxy compound 24.

IR (CHCl_3): 3370 ($\nu_{\text{O-H}}$).

PMR (CDCl_3): 0.6 - 1.1 (br, m, 12H, $-\text{CH}_3$); 1.1 - 1.8 (m, 8H, $-\text{CH}_2$, $-\text{CH}$); 1.90 (br, 2H, D_2O exchangeable, $-\text{OH}$); 3.1 - 3.5 (m, 2H, $-\text{CH}$).

II.A.4.20 Preparation of Diacetate 43



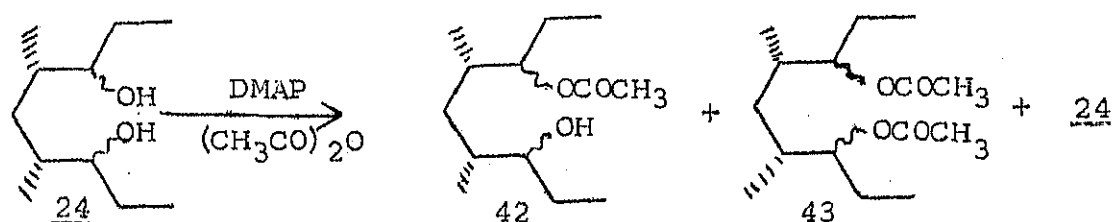
To a solution of 24 (0.056 g, 0.3 mmol) in dichloromethane (2 mL) was added acetic anhydride (0.067 g, 0.66 mmol) and dimethylaminopyridine (0.014 g, 0.12 mmol). The reaction mixture was stirred for 2 h at room temperature. Methanol (0.2 mL) was added and stirred for ten minutes, followed by addition of water. The compound was partitioned between ether and water. The ether layer was dried over anhydrous sodium sulphate, filtered and evaporated to afford an oil which was filtered through a short silica gel column to yield 0.077 g (95%) of diacetate 43.

IR (CHCl_3): 1730 (ν $\begin{smallmatrix} \text{O} \\ \parallel \\ \text{C}-\text{O} \end{smallmatrix}$).

PMR (CCl_4): 0.7 - 1.1 (m, 12H, $-\text{CH}_3$); 1.1 - 2.0 (m, 8H, $-\text{CH}_2$, $-\text{CH}$); 2.03 (s, 6H, $-\text{CH}_3$); 4.72 (m, 2H, $-\text{CH}$).

MS (m/e): 272 (M^+), 242, 214, 152, 111, 70. 55.

II.A.4.21 Preparation of Monoacetate 42



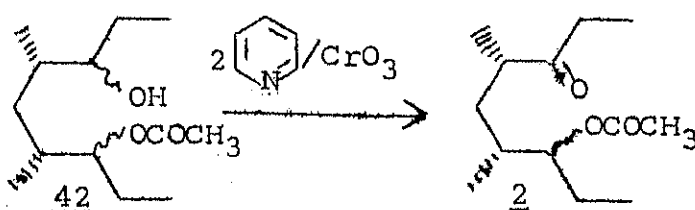
A solution of dihydroxy compound 24, (0.235 g, 1.75 mmol) in dichloromethane (5 mL) was treated with acetic anhydride (0.214 g, 2.1 mmol) and dimethylaminopyridine (0.042 g, 0.35 mmol). The resulting solution was stirred at room temperature for 2 h. Methanol was added (0.5 mL) and stirring was continued for 0.25 h followed by addition of water (15 mL). The organic layer was separated and the aqueous phase was extracted with ether (3x20 mL). The ether extract was washed with brine and dried over anhydrous magnesium sulphate, filtered and evaporated to yield a mixture. The crude product mixture was purified by flash column chromatography to yield 0.047 g (10%) of 43 (elution with 1:9 ether-petroleum ether), 0.253 g of the hydroxyacetate 42 (63%, elution with ether-petroleum ether, 1:1) and 0.055 g (17%) of the unchanged starting material 24 (elution with ether-petroleum ether, 1:1).

Hydroxyacetate 44

IR (CCl_4): 3360 ($\nu_{\text{O-H}}$), 1730 ($\nu_{\text{C=O}}$).

PMR (CCl_4): 0.6–1.06 (m, 12H, $-\text{CH}_3$); 1.1–1.97 (m, 8H, $-\text{CH}_2$, $-\text{CH}$, $-\text{OH}$); 1.05 (s, 3H, $-\text{CH}_3$); 3.36 (m, 1H, $-\text{CH}$); 4.76 (m, 1H, $-\text{CH}$).

MS (m/e): 230 (M^+), 200, 170, 153, 141, 112, 86, 70, 55.

II.A.4.22 Preparation of Ketoacetate 2

To a solution of dry pyridine (0.758 g, 9.6 mmol) in distilled dichloromethane (10 mL) was added chromium trioxide (0.48 g, 4.8 mmol) dried over phosphorus pentoxide in vacuo. Dry celite (0.5 g) was added and the resulting mixture was stirred at 20°C for 0.25 h. A homogeneous burgundy coloured solution was obtained, to which the hydroxyacetate 42 (0.184 g, 0.8 mmol) was added in dichloromethane (0.5 mL) in one portion and the mixture was stirred for 0.5 h. Anhydrous ether was added (50 mL) and the reaction mixture was filtered through a pad of celite and magnesium sulphate. The celite cake was washed thoroughly with ether and the filtrate was evaporated to afford an oil. The crude product was purified by flash column chromatography to yield 0.173 g (95%) of the keto acetate 2 (elution with 1:1 ether-petroleum ether).

IR (CHCl_3): 1730 ($\nu_{\text{C=O}}$), 1705 ($\nu_{\text{C=O}}$).

PMR (CDCl_3): 0.85 (t, 6H, $-\text{CH}_3$, $J = 6$ Hz); 1.03 (d, 6H, $-\text{CH}_3$, $J = 7.5$ Hz); 1.16-1.96 (m, 6H, $-\text{CH}_2$); 2.0 (s, 3H, $-\text{CH}_3$); 2.2-2.8 (m, 2H, $-\text{CH}$); 4.6 (m, 1H, $-\text{CH}$).

MS (m/e): 228 (M^+), 168, 139, 128, 127, 111, 99, 86, 83, 70, 69, 57, 55, 43, 41.

CMR ($\text{CDCl}_3 + \text{CHCl}_3$): 7.84, 9.98, 10.11, 14.73, 15.98, 17.30, 17.98, 21.02, 23.56, 24.36, 33.88, 34.13, 34.29, 34.38, 35.78, 36.61, 43.59, 44.08, 77.32, 79.11, 171.00, 214.71.

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CHAPTER II

(PART B)

ONE POT α -BROMOACETALIZATION OF CARBONYL COMPOUNDS : APPLICATION IN THE SYNTHESIS OF 1,3-DIKETONES

II.B.1 ABSTRACT

The reaction of carbonyl compounds with phenyltrimethylammonium tribromide (PTT) and excess of ethylene glycol in anhydrous tetrahydrofuran has resulted in a simple, one-pot α -bromoacetalization in good yields. The synthetic utility of the α -bromoacetals has been established in the facile synthesis of cyclic 1,3-diketones which are important synthons in organic synthesis. This transformation has been achieved very easily via the formation of olefinic acetals by dehydrobromination followed by oxymercuration-demercuration sequence and subsequent oxidation.

II.B.2 INTRODUCTION

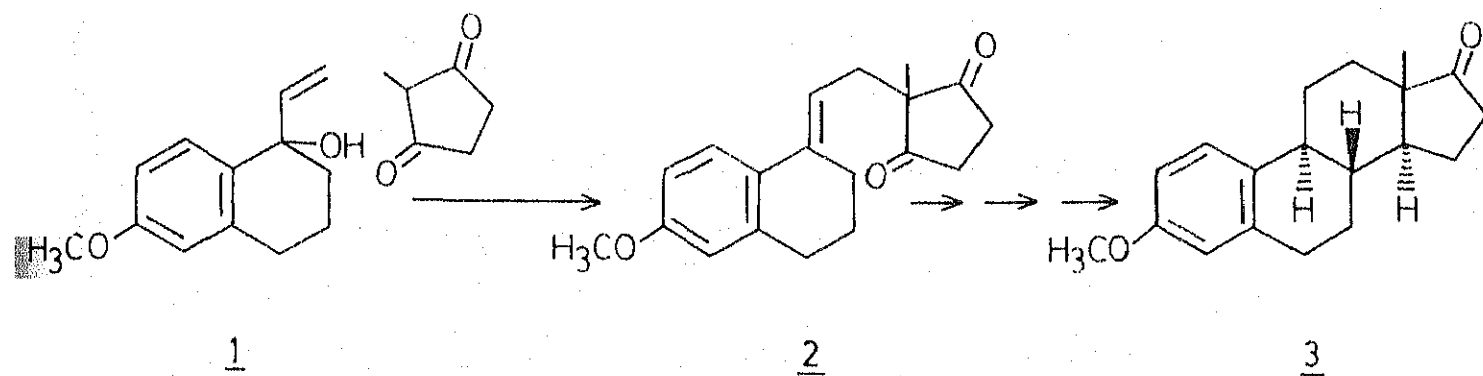
The synthetic utility of α,β -unsaturated carbonyl compounds has enhanced the importance of α -bromoacetals as their valuable precursors.^{1,2} The merits of these synthons over α -halocarbonyl compounds are manifold. For example, α -haloacetals have been successfully utilized in the synthesis of α,β -unsaturated carbonyl compounds,³ whereas, the dehydrohalogenation of α -haloketones in cyclic systems is complicated by side reactions.⁴ Moreover, the basic conditions employed for the dehydrobrominations might also invoke Favorski type of rearrangements in the case of α -haloketones.

In general, α -haloacetals of carbonyl compounds are prepared by a two-step sequence involving bromination of the ketone followed by acetalization^{5,6} or acetalization of the carbonyl compound followed by bromination.^{1,2} It has been observed that the products from these reactions are not usually clean and the yields are only moderate. Marquet *et al.* have reported a convenient procedure for the bromination of acetals using phenyltrimethylammonium tribromide (PTT) in anhydrous tetrahydrofuran. Tetrahydrofuran has been suggested to act as a buffer by reaction with the liberated hydrobromic acid.⁷ A convenient synthesis of α -bromocycloalkanone acetals has been reported, employing bromine and ethylene glycol³ but in this reaction also, the dibromo derivatives are formed as side products. Satoh *et al.* have shown that in the case of

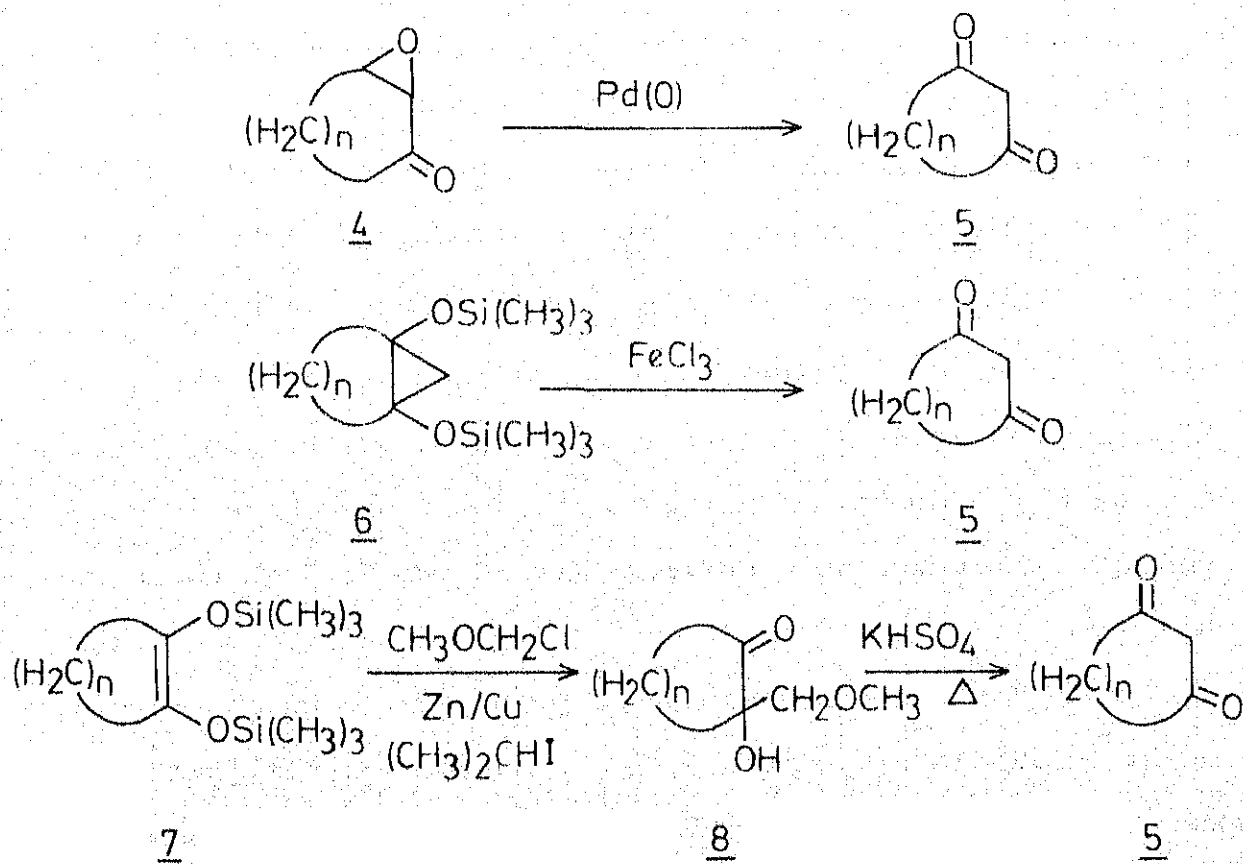
steroidal ketones, α -bromoacetals can be obtained using a very large excess of cupric bromide as the brominating agent in ethylene glycol and p-dioxane.⁸ This procedure is not useful, particularly for medium to large scale preparations. α -Bromoacetals have been synthesized by a combined chemical and electrochemical bromination in which the product was isolated by simple distillation of the reaction mixture without prior aqueous washings.⁹

α,β -Unsaturated acetals, derived from α -bromoacetals are useful synthons, wherein the double bond could be functionalized appropriately to lead to 1,3-diketones. 1,3-Diketones are an important class of compounds in view of the distinct structural properties and high synthetic utility, particularly as building blocks for the elaboration of polycarbocyclic frameworks and heterocyclic nuclei. For example, 1,3-diketones have been used as potential synthons in the total synthesis of several steroidal molecules. Torgov et al. have synthesized estrone methyl ether (3) by an elegant route, involving the alkylation of 2-methyl-1,3-cyclopentanedione with the vinyl alcohol 1 to give the key intermediate 2 (Scheme II.B.1).¹⁰ Similarly, 2-methyl-1,3-cyclohexanedione has been employed in the synthesis of D-homo analogs of the steroidal molecules.¹¹ A number of heterocyclic steroids have also been synthesized by utilizing the 1,3-diketones in building up the molecular skeleton.¹²

Scheme II-B-1



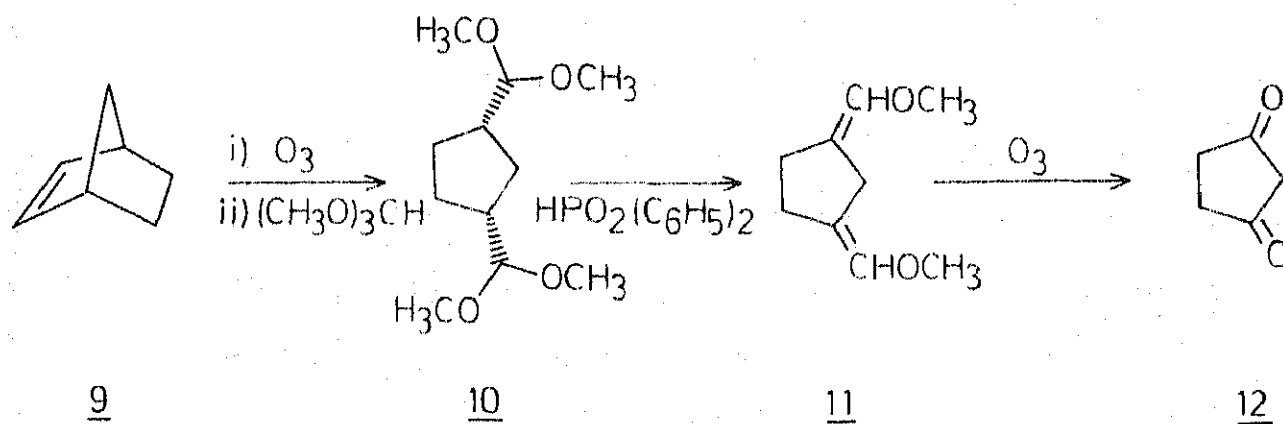
Scheme II-B-2



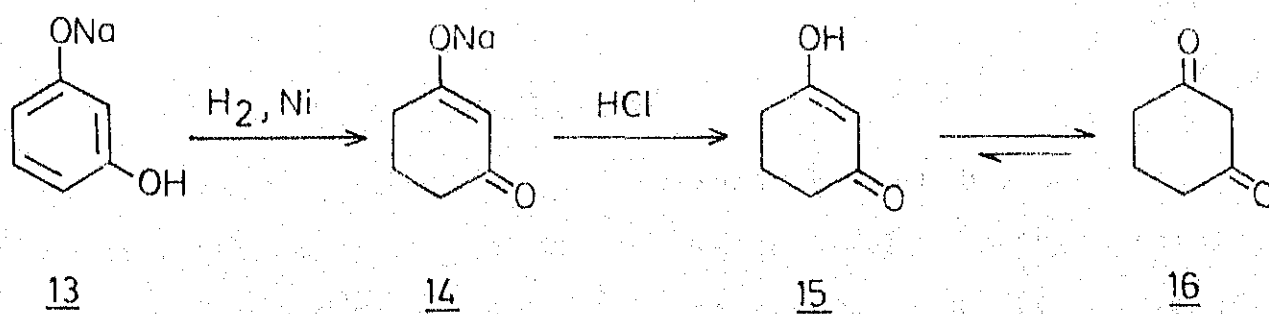
In spite of the high potential of the 1,3-cycloalkadiones in organic synthesis, only a few methods are available for their synthesis. It has been shown that α,β -epoxy ketones give 1,3-diketones in the presence of Pd(0) (Scheme II.B.2).¹³ 1,3-Diketones were also obtained by the reaction of bis(trimethylsilyloxy)bicyclo[n.1.0]alkenes 6 with ferric chloride, followed by treatment with sodium acetate (Scheme II.B.2).¹⁴ Recently, 1,3-cycloalkadiones 5 were synthesized by the reaction of 1,2-bis(trimethylsiloxy)cycloalkenes 7 with chloromethyl methyl ether, followed by treatment of the resulting 2-hydroxy-2-methoxymethylcycloalkanone 8 with potassium hydrogen sulphate (Scheme II.B.2).¹⁵ Synthesis of 2-alkylcyclopentane-1,3-dione and 2-alkylcyclohexane-1,3-dione have been achieved by aluminium chloride mediated cyclization of γ - and δ -ketocarboxylic acids via the acid chlorides.¹⁶

Several syntheses of cyclopentane-1,3-diones which have been reported are rather circuitous.¹⁷⁻¹⁹ A practical and convenient synthesis of cyclopentane-1,3-dione (12) has been reported by Lick and Schank starting from norbornene (9) and using ozonolysis as the key step (Scheme II.B.3).²⁰ The conventional method of obtaining cyclohexane-1,3-dione (16) involves the catalytic hydrogenation of resorcinol in alkaline medium (Scheme II.B.4).²¹ Lumb has achieved the synthesis of 16 under mild conditions using a modified W-6 Raney-nickel catalyst in the hydrogenation of resorcinol.²² The credit for synthesizing cycloheptane-1,3-dione (19) on a preparative scale goes to

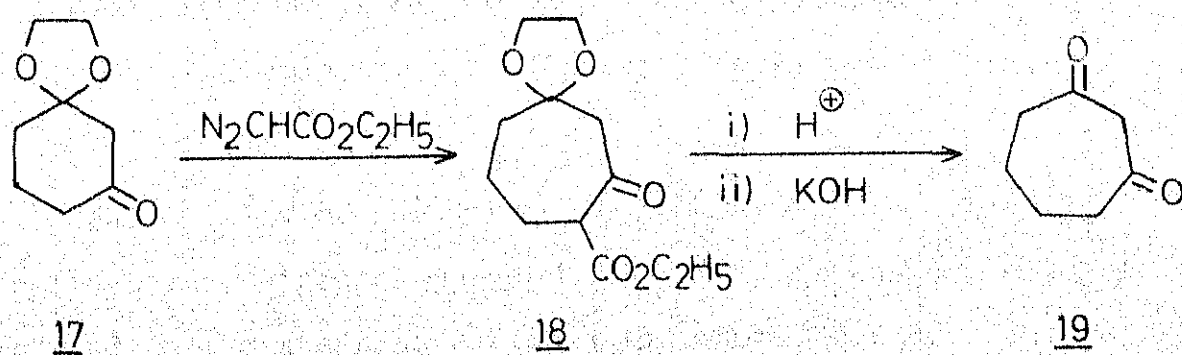
Scheme II-B-3



Scheme II-B-4



Scheme II-B-5



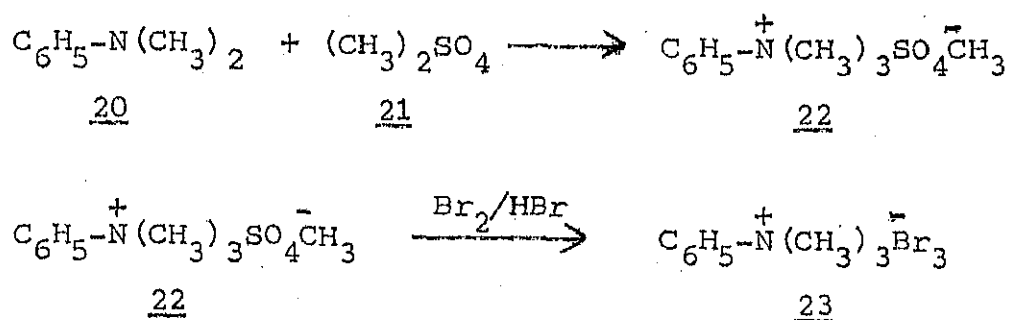
Eistert et al.²³ The compound 19 could be prepared by the catalytic reduction of 2,5,7-tribromohydroxytropone in alkaline medium. A more useful synthesis described by Eistert involves the ring expansion of monoethylene ketal of cyclohexane-1,3-dione 17 using diazoacetic ester, as outlined in Scheme II.B.5.

The objective of the present studies was to develop a mild and versatile procedure for the one-pot synthesis of α -bromoacetals of carbonyl compounds and to explore the utility of these useful synthons in the synthesis of cyclic 1,3-diketones.

II.B.3 RESULTS AND DISCUSSION

In our studies directed towards the synthesis of the insect sex pheromone of the cigarette beetle, in the initial stages, we needed a good supply of 2-bromo-3,3-ethylenedioxy-pentane. In our efforts to synthesize this compound, a mild and versatile procedure for the one-pot α -bromoacetalization of carbonyl compounds was developed using phenyltrimethylammonium tribromide (PTT) and excess of ethylene glycol in tetrahydrofuran.

The utility of phenyltrimethylammonium tribromide (23)²⁴ was first recognized by Marquet et al.⁷ This was conveniently prepared in two steps as outlined in Scheme II.B.6.

Scheme II.B.6

Phenyltrimethylammonium tribromide (23) is remarkably soluble in tetrahydrofuran (630 g/L at 20°C) and is a source of Br_3^- ions whose properties are different from those of molecular bromine. In particular, it is much less electrophilic than bromine and less reactive towards aromatic rings and non-enolic double bonds.²⁵ Thus PTT (23) has been used as a selective brominating agent of ketones and dioxolanes when the molecule bears double bonds or activated aromatic nuclei.²⁶ The "active bromine" present in PTT (23) could be determined by titration against sodium thiosulphate solution.

In our attempts to bring about one-pot α -bromoacetalization, initially, we focussed our attention on simple symmetric molecules like acetone (24) and 3-pentanone (26). When acetone was treated with PTT (3 equivalents) and excess of ethylene glycol in anhydrous tetrahydrofuran, at room temperature for 20 h, excellent yield (90%) of bromoacetal 25 was obtained, b.p. 69-70°C (14 mm), [lit.²⁷ b.p. 73-74°C (18 mm)]. The PMR spectrum showed a singlet at δ 1.57 (3H) corresponding to the

methyl protons, another singlet at 3.36 (2H) due to the methylene protons and yet another singlet at 3.96 (4H) assigned to the ethylenedioxy protons (Fig. II.B.1). The mass spectrum showed two peaks at 165 and 167 ($M^+ - CH_3$). When 3-pentanone was treated with PTT (1.5 equivalents) under similar conditions for 24 h, bromoacetal 27 resulted in 89% yield, b.p. 64-68°C (2.5 mm) [lit.²⁸ b.p. 60-68°C (3 mm)].

The reaction of an unsymmetrical ketone, 2-butanone (28) with PTT and ethylene glycol in tetrahydrofuran gave a mixture of 1-bromo and 3-bromo acetals (29a and 29b) in 74% yield, b.p. 74-80°C (12 mm) [lit.²⁹ b.p. 75-77 (12 mm)]. When pinacolone (30) was treated with PTT under analogous conditions, the reaction proceeded smoothly to yield 82% of pure bromoacetal 31, b.p. 85-90°C (15 mm). The PMR spectrum of 31 showed a singlet at δ 1.0 (9H) corresponding to the tert-butyl group protons and another singlet at 3.7 (2H) due to the methylene protons. The ethylenedioxy group protons indicated a multiplet centred at 4.33 (4H) (Fig. II.B.2). The mass spectrum showed peaks at 167 and 169 ($M^+ - C_4H_9$).

Having successfully achieved the α -bromoacetalization of acyclic carbonyl compounds, we next directed our attention towards the cyclic ketones of various ring sizes. When cyclopentanone (32) was treated with PTT and ethylene glycol in tetrahydrofuran, α -bromoacetal 33 was obtained in excellent yield (90%), b.p. 95-100°C (15 mm). Similarly, when cyclohexanone (34) was subjected to identical reaction conditions, a

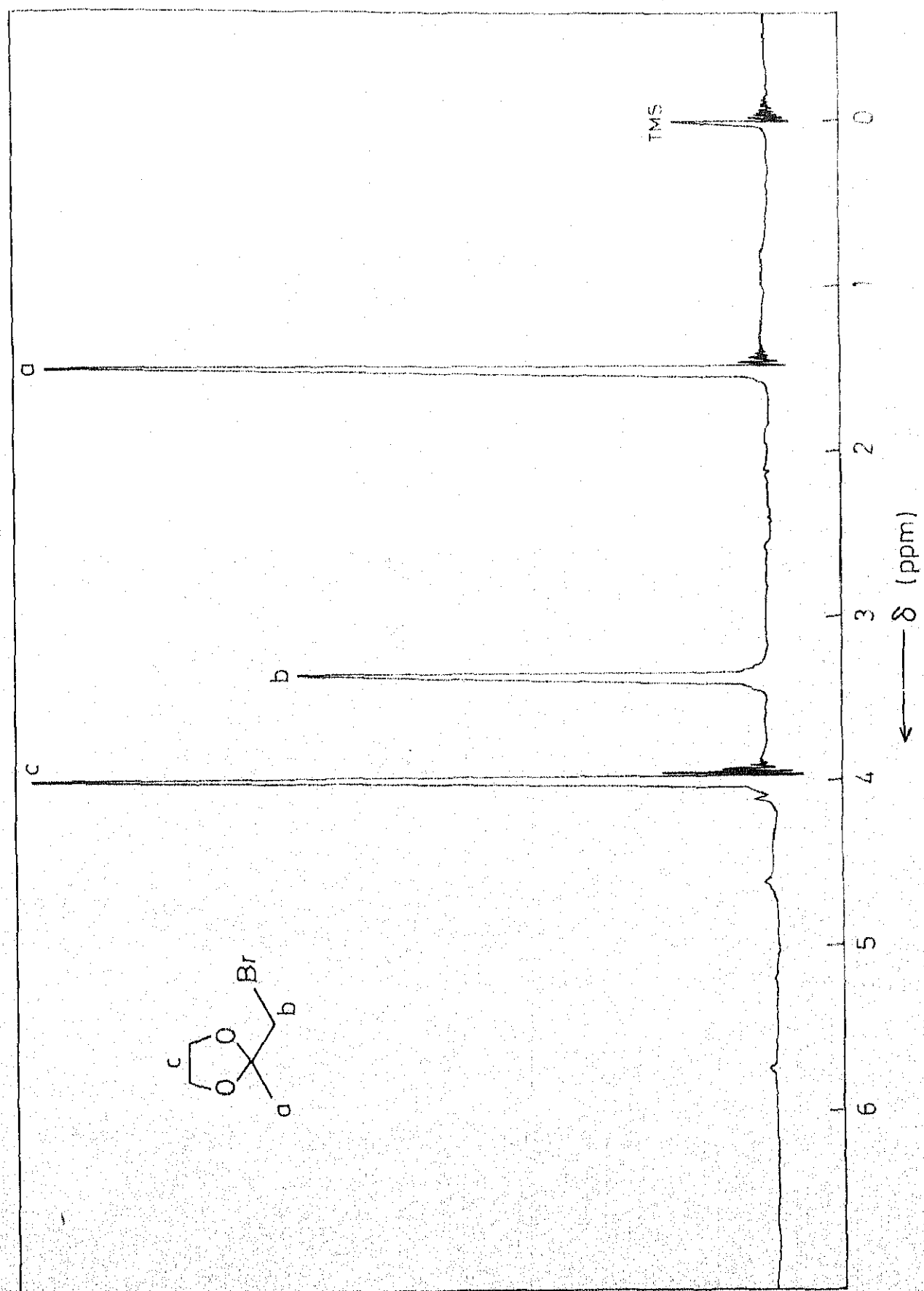


Fig. II-B.1 ^1H NMR spectrum (60 MHz) of 25.

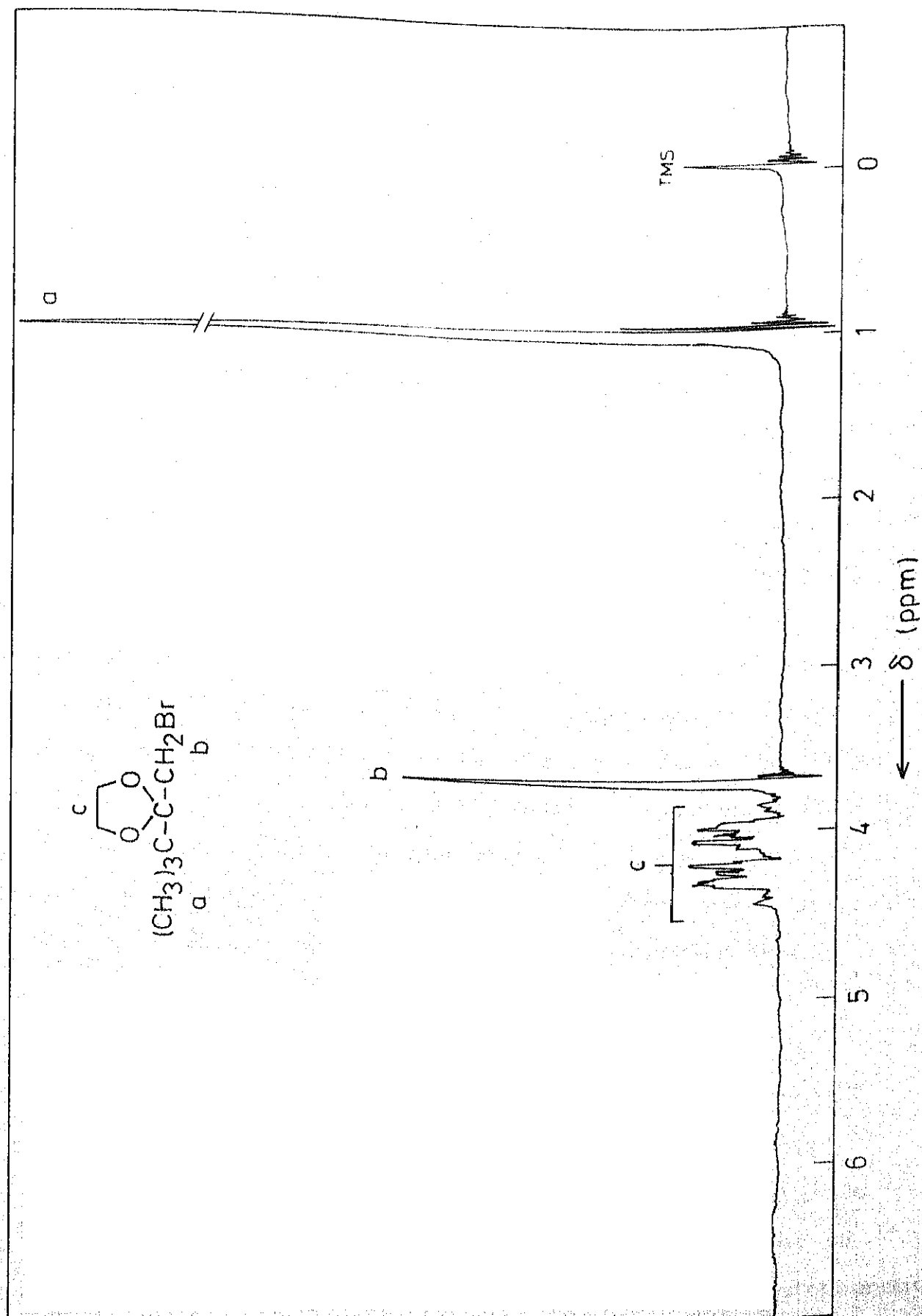


Fig. II.B.2 ^1H NMR spectrum (60 MHz) of 31

clean product 35 was isolated (89%), b.p. 90-92°C (5 mm) [lit.⁵ b.p. 115-116°C (10 mm)]. Cycloheptanone (36) under similar conditions yielded 81% of the α -bromoacetal 37, b.p. 77-80°C (0.5 mm) [lit.³ b.p. 79-83°C (0.5 mm)]. A remarkable selectivity was observed in the reaction of 2-methylcyclohexanone (38). Under the conditions of bromoacetalization, the bromoacetal 39 was obtained as the only product in 79% yield. The PMR spectrum showed a singlet at δ 1.76 (3H) assigned to the methyl protons and a multiplet between 1.4 and 2.3 for the methylene protons. A singlet appeared at 4.03 (4H) due to the ethylenedioxy protons (Fig. II.B.3). The mass spectrum showed molecular ion peaks at 234 and 236 (M^+). When the reaction was worked up after 15 h, the crude product was found to be a mixture of the bromoacetal 39 and the unbrominated acetal. In order to get an insight into the mode of α -bromoacetalization, reactions were carried out with 2-methylcyclohexanone (38) and cyclopentanone (32) for a shorter period of time (5-6 h). It was observed that the unbrominated acetals were the major products. Therefore, it is reasonable to assume that one-pot α -bromoacetalizations involve acetalization and then bromination of acetals as the major reaction pathway. The compound 38 afforded 65% of the acetal in 6 h and 32 yielded 68% of the acetal in 5 h.

It has been well established that PTT is less electrophilic and does not attack aromatic systems.⁷ In order to substantiate this, one-pot α -bromoacetalization of acetophenone

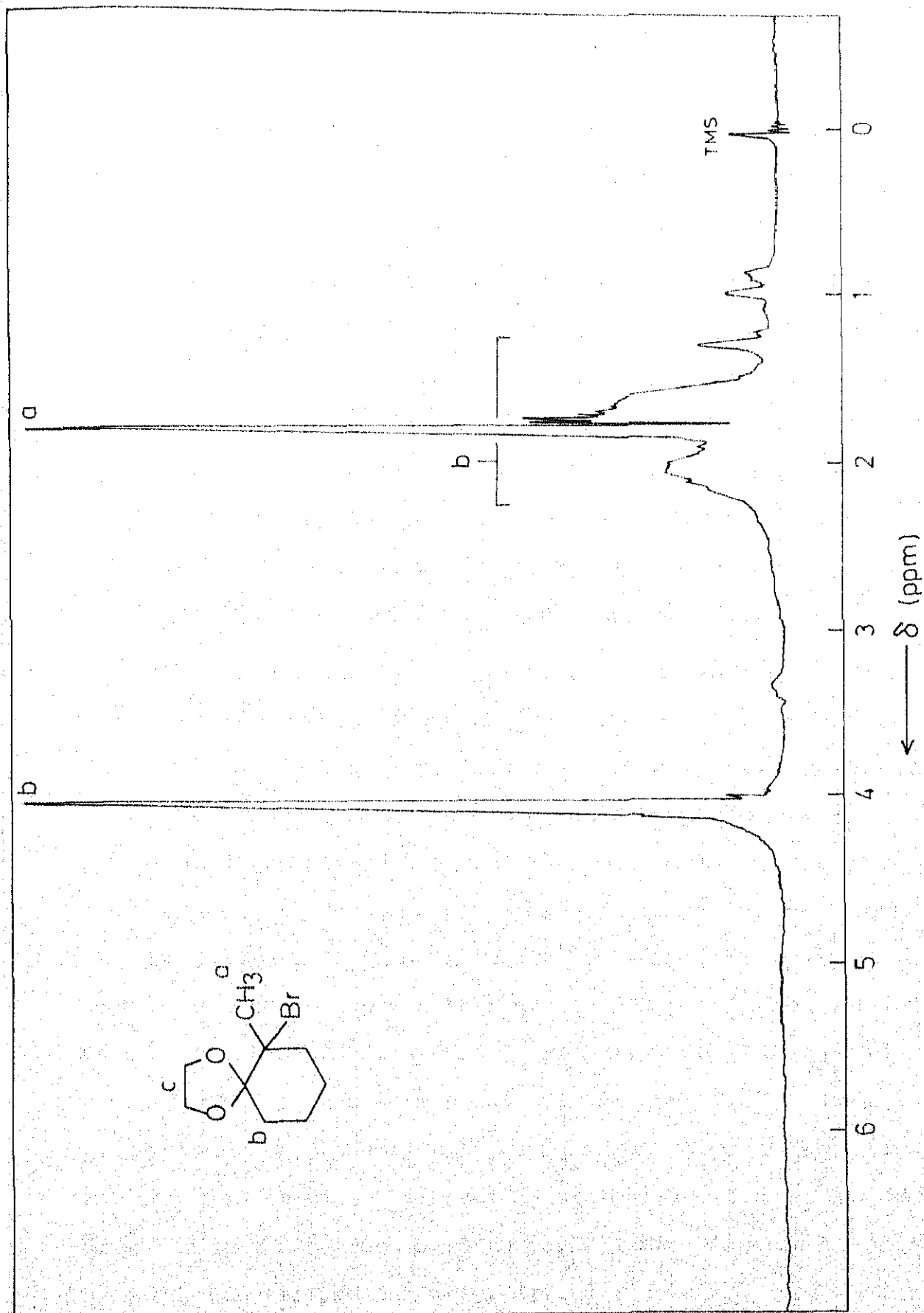







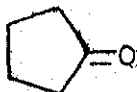
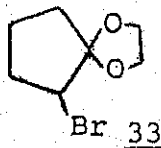
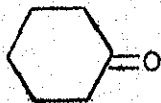
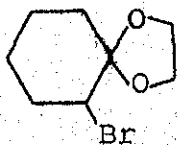
Fig. II-B-3 ¹H NMR spectrum (60 MHz) of 35.

(40) was attempted using PTT and ethylene glycol in tetrahydrofuran. The reaction was completed in 22 h at room temperature to yield 82% of the bromoacetal 41, m.p. 61°C (Lit.⁷ m.p. 61°C).

From the several cases of carbonyl compounds studied, it has been observed that bromoacetals are formed and isolated in high yield using the one-pot α -bromoacetalization procedure (Table II.B.1). Next, we decided to explore the potential usefulness of these α -bromoacetals as valuable synthons by extending the methodology to synthesize cyclic 1,3-diketones through the formation of unsaturated acetals, followed by appropriate functionalization of the double bond (Scheme II.B.7).

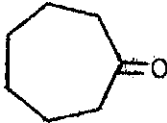
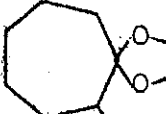
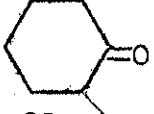
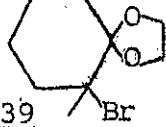
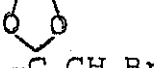
The bromoacetal 35 was selected as the representative example to study this methodology and to optimize the conditions. Potassium tert-butoxide or sodium methoxide in dimethyl sulphoxide has been found to yield the dehydrobrominated product rapidly at room temperature from α -bromoacetals.³ When bromoacetal 35 was treated with potassium tert-butoxide (1.5 equivalents) in dimethyl sulphoxide at room temperature for 6 h, the unsaturated acetal 42b was obtained in 80% yield, b.p. 74-76°C (17 mm) [lit.³ b.p. 86.5 - 88.5°C (23 mm)]. The PMR spectrum showed a multiplet between δ 1.06 and 2.4 (6H) due to the methylene protons. A slightly split singlet appeared at 3.83 (4H) corresponding to the ethylenedioxy protons and two groups of signals appeared between 5.28 and 5.88 (2H) which can be assigned to the vinylic protons (Fig. II.B.4).

Table II.B.1 α -Bromoacetalization of Carbonyl Compounds

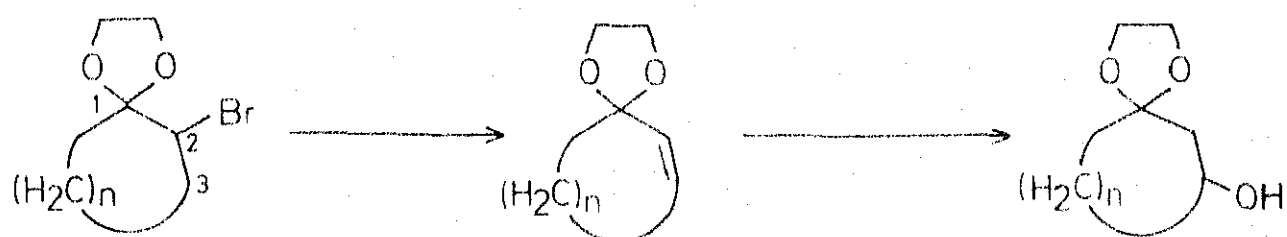
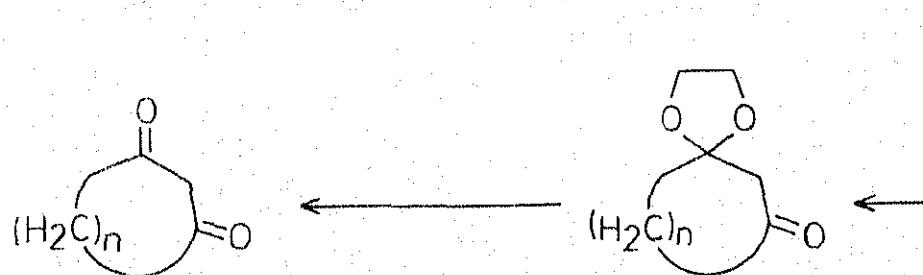
Sl. No.	Substrate	Product	Reaction time (h)	Yield (%)
1.	CH_3COCH_3 <u>24</u>	 $\text{CH}_3\text{-C-CH}_2\text{Br}$ <u>25</u>	20	90
2.	$\text{C}_2\text{H}_5\text{COC}_2\text{H}_5$ <u>26</u>	 $\text{C}_2\text{H}_5\text{-C-CHBrCH}_3$ <u>27</u>	24	89
3.	$\text{C}_2\text{H}_5\text{COCH}_3$ <u>28</u>	 $\text{CH}_3\text{CHBr-C-CH}_3$ <u>29b</u>  + $\text{C}_2\text{H}_5\text{-C-CH}_2\text{Br}$ <u>29a</u>	24	74
4.	$(\text{CH}_3)_3\text{CCOCH}_3$ <u>30</u>	 $(\text{CH}_3)_3\text{C-C-CH}_2\text{Br}$ <u>31</u>	22	82
5.	 <u>32</u>	 <u>33</u>	24	90
6.	 <u>34</u>	 <u>35</u>	27	89

...contd.

Table II.B.1 (contd.)

Sl. No.	Substrate	Product	Reaction time (h)	Yield (%)
7.	 <u>36</u>	 <u>37</u>	30	81
8.	 <u>38</u>	 <u>39</u>	28	79
9.	$\text{C}_6\text{H}_5\text{COCH}_3$ <u>40</u>	 <u>41</u>	22	82

Scheme II.B.7

33 $n = 2$ 35 $n = 3$ 37 $n = 4$ 42 a) $n = 2$ b) $n = 3$ c) $n = 4$ 43 a) $n = 2$ b) $n = 3$ c) $n = 4$ 12 $n = 2$ 16 $n = 3$ 19 $n = 4$ 44 $n = 2$ 17 $n = 3$ 45 $n = 4$

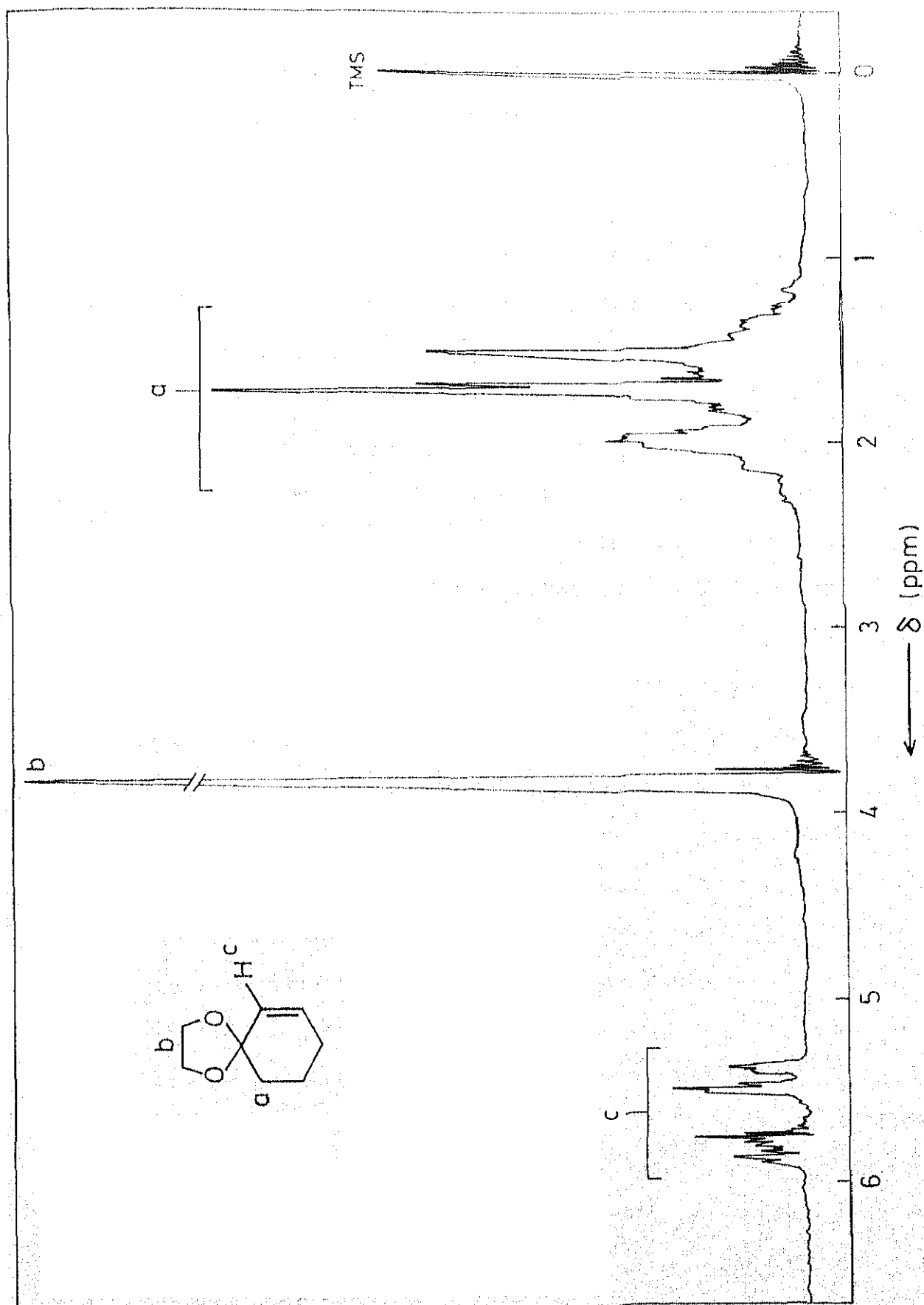


Fig. II.B.4 ^1H - NMR spectrum (60 MHz) of 42b.

Initial efforts to hydrate the double bond using hydroboration methods did not give encouraging results, yielding a mixture of products. In recent years, oxymercuration and demercuration has been effectively used for Markownikoff hydration of carbon-carbon double bonds.³⁰ Johnson *et al.*, during their studies of solvent effects in the oxymercuration of 2-cyclohexenol and related systems have found that trans-3-hydroxy product is the major product in such reactions when performed in acetonitrile-water system (95:5).³¹ When the unsaturated acetal 42b was treated with mercuric acetate in acetonitrile-water (95:5) medium, followed by treatment with alkaline sodium borohydride, 3-hydroxyacetal 43b was obtained in 70% yield after flash chromatography.

Attempted oxidation of the hydroxyacetal 43b with silver carbonate-celite³² and pyridinium dichromate³³ was not very effective. When the compound 43b was treated with chromium trioxide-pyridine complex³⁴ at room temperature, the reaction was complete within 0.25 h to give the product 17 in 55% yield. When the same reaction was performed in the presence of dry celite, there was a remarkable improvement in the yield of the keto-acetal 17 (86%). The IR spectrum indicated a strong absorption at 1720 cm^{-1} characteristic of the six membered ketone. The PMR spectrum distinctly showed the presence of three types of methylene groups, thereby confirming the compound to be a 1,3-keto-acetal. A broad singlet appeared at $\delta 1.66$ (4H) corresponding to the methylene protons and another broad singlet at 2.06 (2H)

due to the methylene protons adjacent to the carbonyl group. The methylene protons in between the ketone and the acetal groups showed a sharp singlet at 2.26 (2H) and the ethylenedioxy group protons traced a singlet at 3.76 (4H) (Fig. II.B.5).

When a solution of ketoacetal 17 in ether was stirred with a drop of concentrated hydrochloric acid, a fairly clean reaction occurred to give 1,3-cyclohexanedione (16), m.p. 105-106°C (lit.²¹ m.p. 105-107°C). But the isolation of the dione was slightly complicated due to its solubility in water. In order to carry out this deacetalization under milder conditions, the procedure reported by Huet *et al.* was attempted³⁵ by stirring the ketoacetal 17 with silica gel impregnated with 15% sulphuric acid in dichloromethane for 24 h at room temperature. Though the reaction took a longer time, isolation and purification problems were minimized by this method and 78% yield of the dione 16 was obtained. An authentic sample of 16 was prepared by the lithium-liquid ammonia reduction of resorcinol dimethyl ether, followed by hydrolysis of the enol ether and compared with the synthesized 1,3-dione 16.

Next, we focussed our attention on the synthesis of cycloheptane-1,3-dione (19), applying the same methodology. The unsaturated acetal 42c was obtained in 70% yield by dehydrobromination of bromoacetal 37 with potassium *tert*-butoxide in dimethyl sulphoxide, b.p. 94-96°C (10 mm) [lit.³ b.p. 67°C (2.4 mm)]. The unsaturated acetal 42c showed a broad multiplet between δ 1.4 and 2.5 (8H) due to the methylene protons, a multiplet at

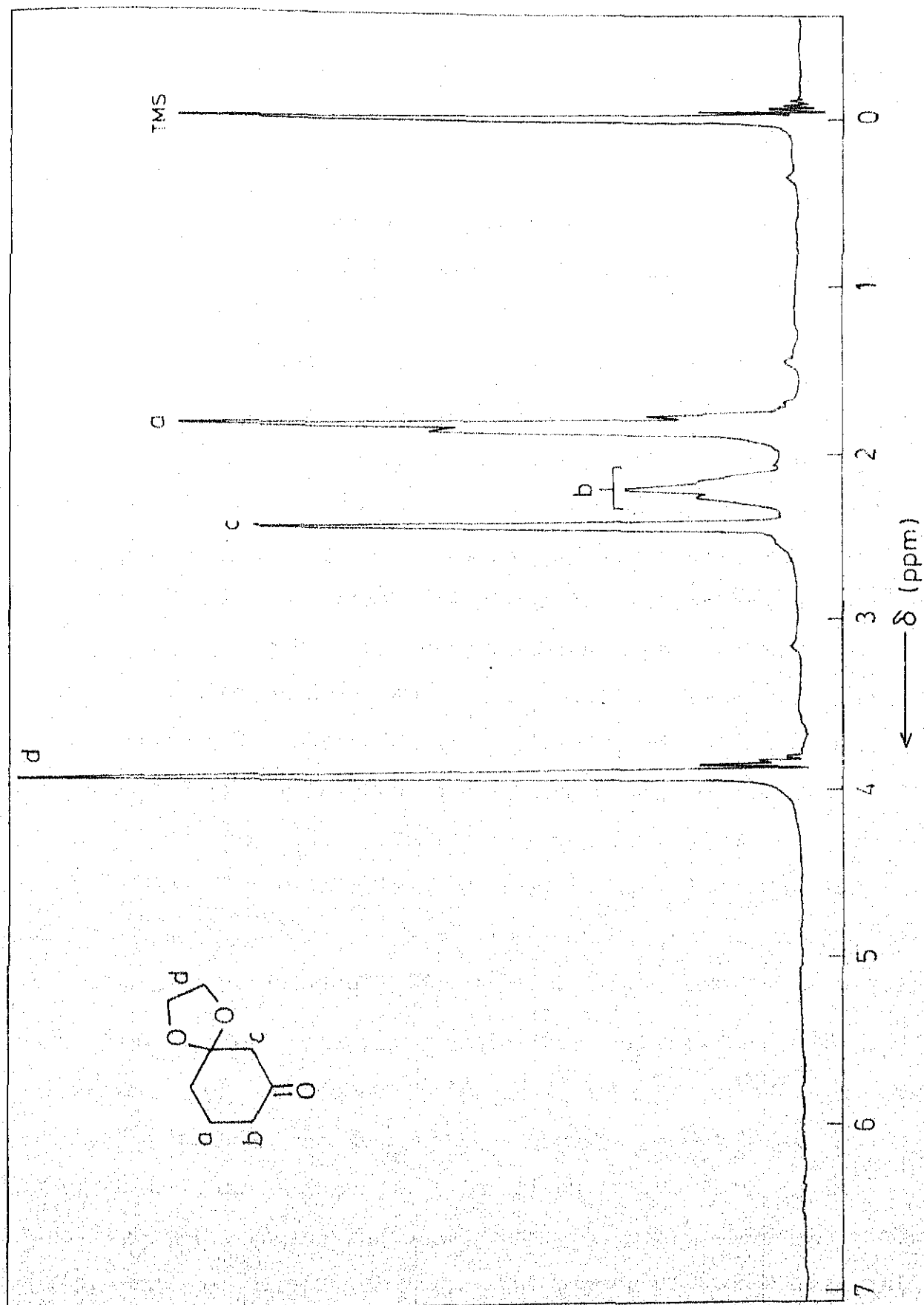


Fig. II-B.5 ^1H NMR spectrum (90 MHz) of **17**.

3.8 (4H) assigned to the ethylenedioxy protons and a multiplet centred at 5.66 (2H) corresponding to the vinylic protons (Fig. II.B.6). The oxymercuration-demercuration was performed on this unsaturated acetal 42c to yield 64% of the hydroxyacetal 43c. The oxidation of 43c using chromium trioxide-pyridine complex in dichloromethane gave 70% of the ketoacetal 45. The IR spectrum of 45 showed a strong absorption at 1700 cm^{-1} characteristic of the seven-membered ketone. The PMR spectrum showed a broad signal at $\delta 1.66$ (6H) corresponding to the methylene protons. The methylene protons adjacent to the carbonyl group indicated a broad singlet at 2.23 (2H) and the methylene protons flanked by the ketone and the acetal groups traced a sharp singlet at 2.56 (2H). The ethylenedioxy group protons showed again a singlet at 3.76 (4H) (Fig. II.B.7). Treatment of 45 with silica gel impregnated with 15% sulphuric acid, in dichloromethane did result in the deprotection of the acetal, but the reaction was very slow (70 h). However, when 45 was treated with 10% hydrochloric acid, cycloheptane-1,3-dione (19) was obtained in very good yield (75%), characterized as its disemicarbazone, m.p. $204\text{--}206^\circ\text{C}$ (dec.) [lit.²³ m.p. $205\text{--}206^\circ\text{C}$ (dec.)].

Encouraged by the success in the synthesis of cyclohexane-1,3-dione (16) and cycloheptane-1,3-dione (19), we directed our attention towards the synthesis of cyclopentane-1,3-dione. The unsaturated acetal was readily obtained in 70% yield by the dehydrobromination of the bromoacetal 33, b.p. $64\text{--}66^\circ\text{C}$ (21 mm), [lit.³ b.p. $65\text{--}66.5^\circ\text{C}$ (22 mm)]. The oxymercuration-demercuration

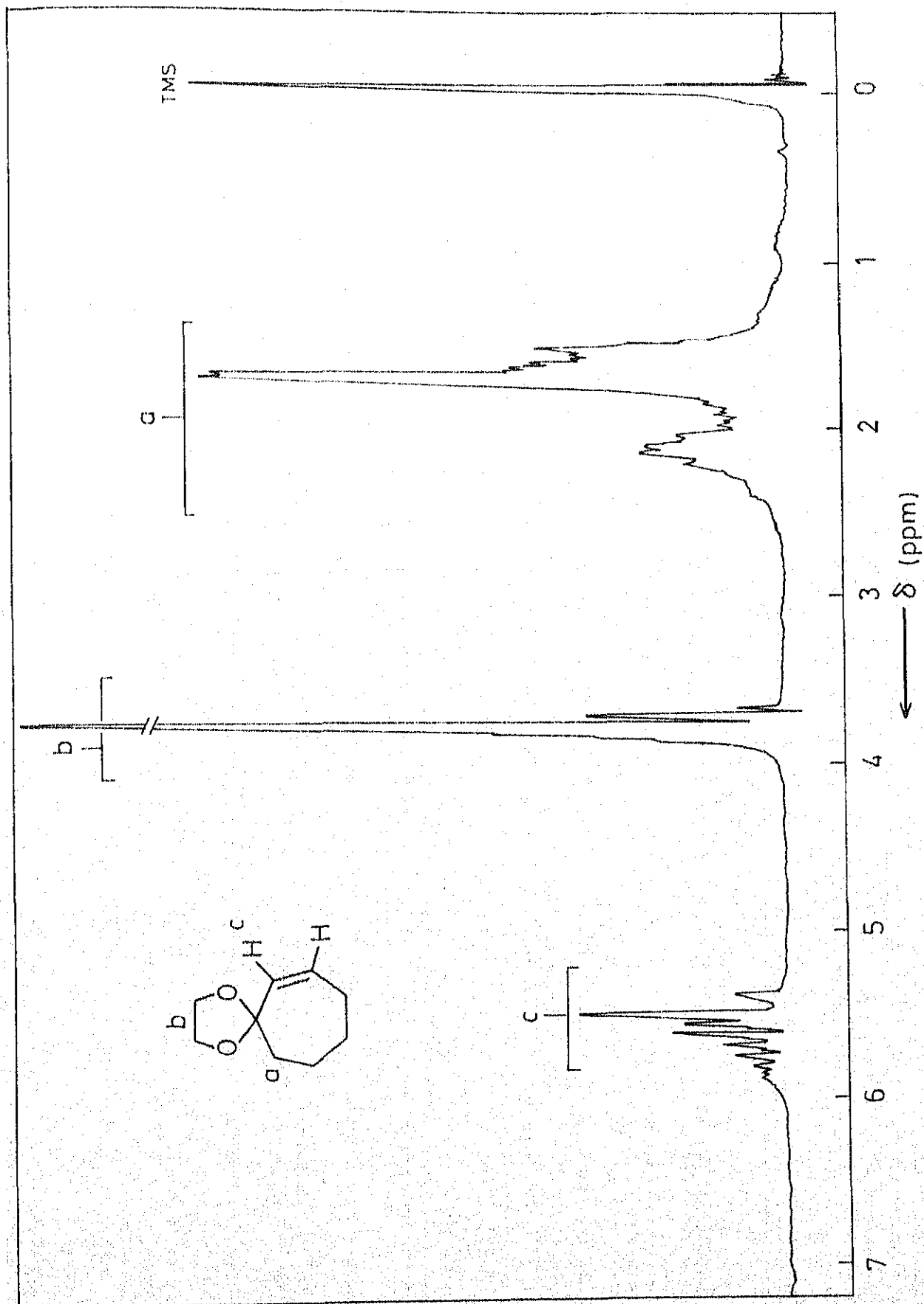


Fig. II.B-6 ^1H NMR spectrum (90 MHz) of 42c.

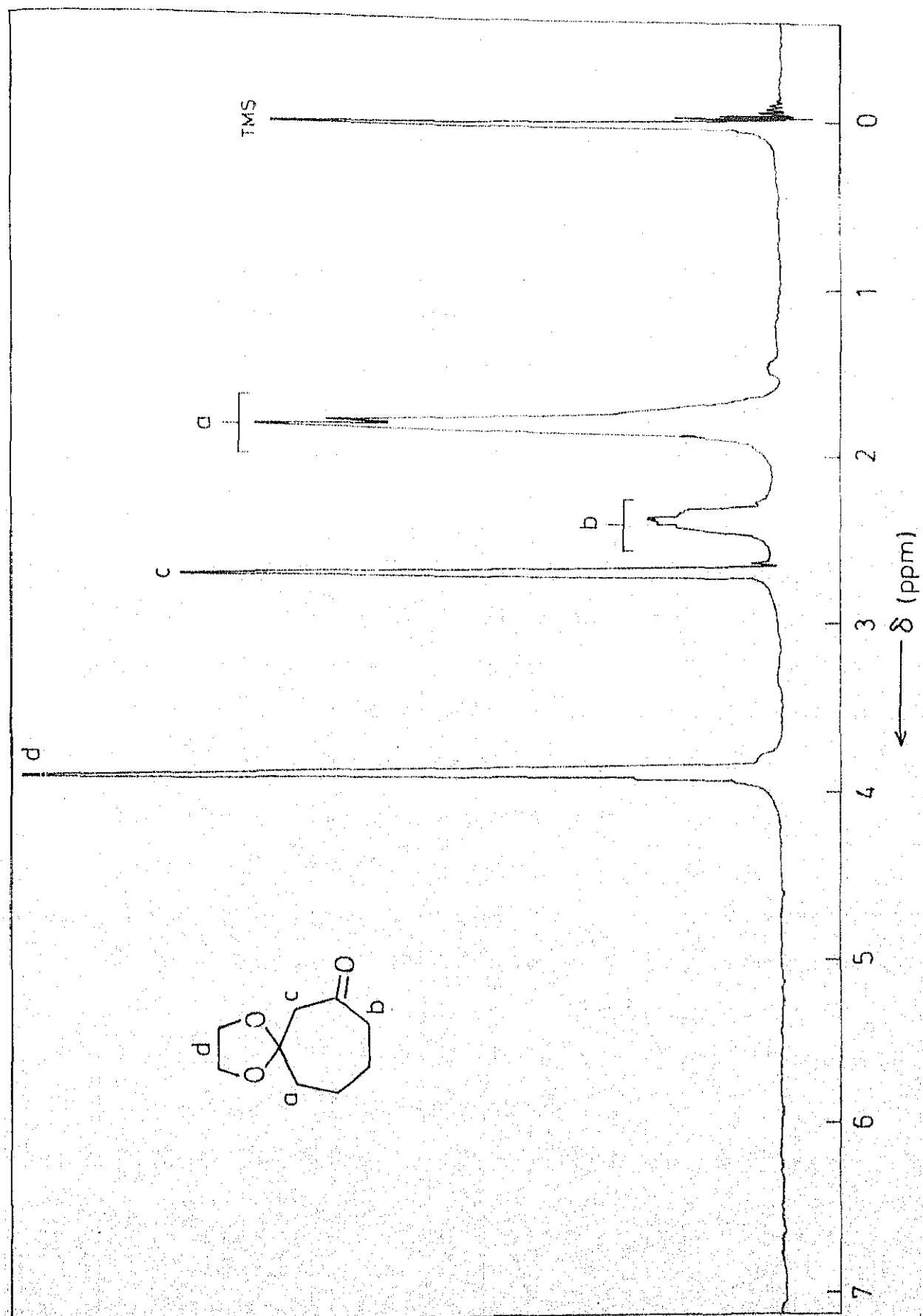


Fig. II.B.7 ^1H NMR spectrum (90 MHz) of 45.

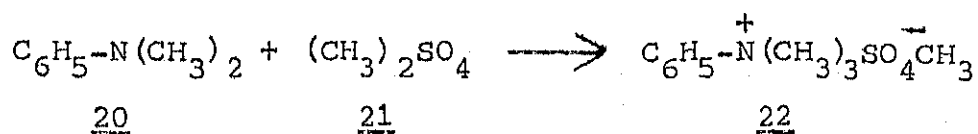
procedure gave a very poor yield of a mixture of products. Efforts to improve the reaction using water-tetrahydrofuran solvent system and excess of sodium borohydride in the place of sodium hydroxide solution, proved futile. Attempts to hydrate the double bond using palladium chloride catalyzed addition of water³⁶ in the presence of oxygen was also unsuccessful. Reaction conditions are yet to be worked out for achieving this transformation.

The unsaturated acetal 42a seems to be a promising synthon. Smith *et al.* have synthesized a series of (+)-pentenomycins I-III, epipentenomycins and dehydropentenomycin using a common synthetic precursor, 2-(hydroxymethyl)-2-cyclopentenone.³⁷ It appears feasible that this key intermediate could be synthesized by the hydroxymethylation of the unsaturated acetal 42a.³⁸

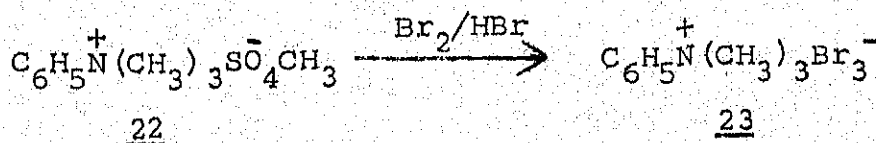
Although many methods are known for the synthesis of α -bromoacetals of carbonyl compounds, the present procedure offers versatility, mildness and selectivity. The methodology developed to achieve the synthesis of cyclic 1,3-diketones is very simple and thus we have a convenient procedure for the overall conversion of inexpensive and readily available ketones to useful synthons like 1,3-diketones.

II.B.4 EXPERIMENTAL

General procedures adopted for the reactions, purification of solvents and reagents were the same as are outlined in II.A.4. Dimethyl sulphate was purified as recommended.³⁹ Potassium tert-butoxide was prepared according to the reported procedure.⁴⁰ Acetonitrile was distilled from phosphorus pentoxide and stored over 4A Type molecular sieves. Mercuric acetate was purified by recrystallising from hot water containing 5% acetic acid.

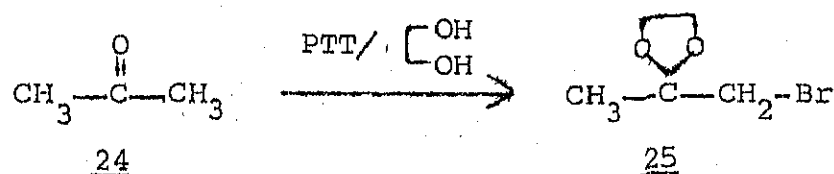
II.B.4.1a Preparation of Phenyltrimethylammonium sulphomethylate

To a stirred solution of freshly distilled dimethylaniline (20, 24 g, 26 mL, 200 mmol) in toluene (100 mL) was added distilled dimethylsulphate (21, 25.2 g, 19 mL, 200 mmol) at ca. 40°C dropwise in 0.3 h. A colourless sulfomethylate started crystallising after a few minutes. Stirring was continued for 1.5 h at ca. 50°C and then for 1 h at 100°C. The reaction mixture was cooled and the product was filtered, washed with dry toluene and dried in vacuo to yield 47.5 g (96%) of the sulphomethylate 22.

II.B.4.1b Preparation of Phenyltrimethylammonium tribromide
(23, PTT)

To a solution of sulphomethylate 22 (45 g, 180 mmol) in aqueous hydrobromic acid (48%, 45 mL) diluted with water (45 mL), added bromine dropwise (38.75 g, 12.5 mL, 244 mmol) over a period of 0.75 h under magnetic stirring. The orange yellow precipitate which was formed was stirred at room temperature for 5-6 h. The product was filtered, washed with water (30 mL) and air dried. The crude product was recrystallised from acetic acid (100 mL) to yield 63.8 g, (93%) of PTT, m.p. 115-166°C, (lit.²⁴ m.p. 115-116°C).

II.B.4.2 α -Bromoacetalization of Acetone (24)



To a stirred solution of acetone (1.74 g, 30 mmol) in tetrahydrofuran and ethylene glycol (30 mL + 30 mL) was added phenyltrimethylammonium tribromide (23, 22.5 g, 60 mmol). The stirring was continued at room temperature for 20 h. The reaction mixture was then poured into a solution of 10% sodium bicarbonate (250 mL) and 5% sodium thiosulphate (25 mL) and extracted with ether (2 x 100 mL). The combined organic extract was washed with water (2 x 100 mL), followed by brine (100 mL) and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to yield the bromoacetal 25 which was distilled to give 4.86 g (90%) of 42, b.p. 69-70°C

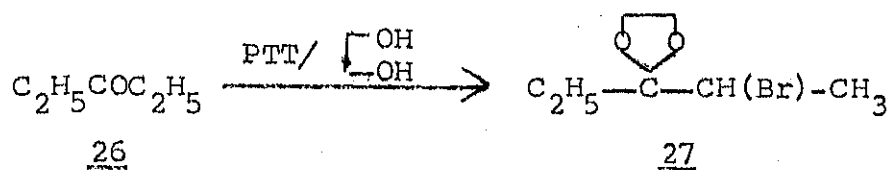
(14 mm), [lit.²⁷ b.p. 73-74°C (18 mm)].

IR (thin film): 1120, 1080, 1040 ($\nu_{\text{C-O-C}}$).

PMR (CDCl_3): 1.57 (s, 3H, $-\text{CH}_3$); 3.36 (s, 2H, $-\text{CH}_2-\text{Br}$); 3.96 (s, 4H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$).

MS (m/e): 167, 165 (M^+-15), 151, 149, 137, 136, 135, 134, 123, 121, 105, 95, 93, 87.

II.4.3 α -Bromoacetalization of 3-Pentanone (26)



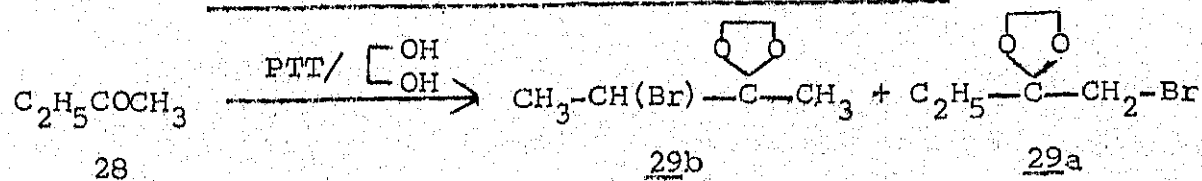
The reaction was carried out as above with 3-pentanone (4 g, 46 mmol), PTT (19.2 g, 51 mmol) and ethylene glycol (40 mL) in tetrahydrofuran (40 mL) at room temperature for 24 h to yield 8.5 g (89%) of 27, b.p. 64-68°C (2.5 mm) [lit.²⁸ b.p. 60-68°C (3 mm)].

IR (thin film): 1140, 1050, 1030 ($\nu_{\text{C-O-C}}$).

PMR (CDCl_3): 0.8-1.0 (t, 3H, $-\text{CH}_3$); 1.6-2.0 (m, 5H, $-\text{CH}_3$, $-\text{CH}_2$); 4.0-4.6 (m, 5H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$, $-\text{CH}-\text{Br}$).

MS (m/e): 181, 179 (M^+), 129, 127, 115, 113, 109, 107, 103, 101, 99, 88, 87, 86, 73.

II.B.4.4 α -Bromoacetalization of 2-Butanone (28)



The reaction was carried out under identical conditions as above with 2-butanone (28, 0.72 g, 10 mmol), PTT (4.51 g, 12 mmol) and ethylene glycol (12 mL) in tetrahydrofuran (12 mL) to yield 1.44 g of a mixture of products, 29a and 29b (74%), b.p. 74-80°C (12 mm), [lit.²⁹ b.p. 75-77°C (12 mm)].

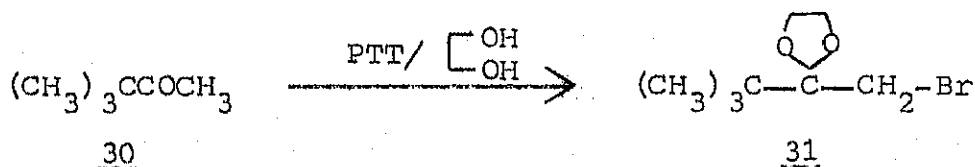
IR (thin film): 1100, 1060 ($\nu_{\text{C-O-C}}$).

PMR (CDCl_3): 0.96 (t, $-\text{CH}_3$); 1.5 (s, $-\text{CH}_3$); 1.76 (d, $-\text{CH}_3$); 1.8 (q, $-\text{CH}_2$); 3.4 (s, $-\text{CH}_2$); 4.03 (m, 4H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$).

Anal. for $\text{C}_6\text{H}_{11}\text{O}_2\text{Br}$: Calcd. C, 36.92; H, 5.64.

Found C, 36.78; H, 5.74.

II.B.4.5 α -Bromoacetalization of 3,3-Dimethyl-2-butanone (30)



The reaction was performed under analogous conditions as above with tert-butyl methyl ketone (30, 0.5 g, 5 mmol). PTT (2.82 g, 7.5 mmol) and ethylene glycol (6 mL) in tetrahydrofuran (6 mL) for 22 h which yielded 0.914 g (82%) of 31, b.p. 85-90°C (15 mm).

IR (thin film): 1170, 1060 ($\nu_{\text{C-O-C}}$).

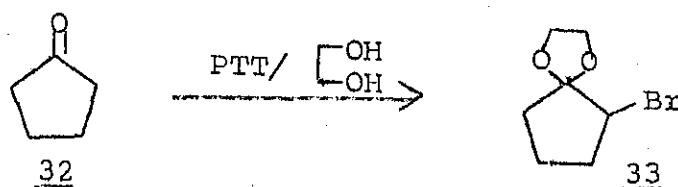
PMR (CDCl_3): 1.0 (s, 9H, $-\text{CH}_3$); 3.7 (s, 2H, $-\text{CH}_2-\text{Br}$); 4.33 (m, 4H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$).

MS (m/e): 167, 165 ($\text{M}^+-\text{C}_4\text{H}_9$), 123, 121, 86, 73, 57.

Anal. for $C_8H_5O_2Br$: Calcd. C, 43.04; H, 6.73.

Found C, 43.11; H, 6.80.

II.B.4.6 α -Bromoacetalization of Cyclopentanone (32)



The reaction was carried out as in the earlier cases with 32 (4.2 g, 50 mmol), PTT (19.2 g, 51 mmol) and ethylene glycol (40 mL) in tetrahydrofuran (40 mL) for 24 h to yield 9.2 g of 33 (90%), b.p. 95-100°C (15 mm).

IR (thin film): 1110, 1060, 1035, 1010 (ν_{C-O-C}).

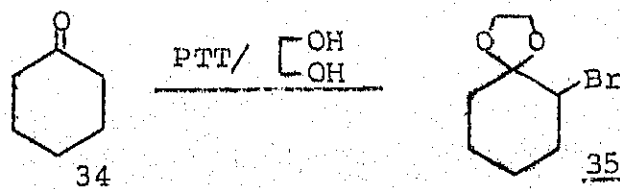
PMR ($CDCl_3$): 1.56-2.6 (m, 6H, $-CH_2-$); 4.03 (m, 5H, $-O-CH_2-CH_2-O-$, $-CH-Br$).

MS (m/e): 208, 206 (M^+), 179, 177, 137, 135, 127, 125, 99.

Anal. for $C_7H_{11}O_2Br$: Calcd. C, 40.58; H, 5.31.

Found C, 40.26; H, 5.18.

II.B.4.7 α -Bromoacetalization of Cyclohexanone (34)



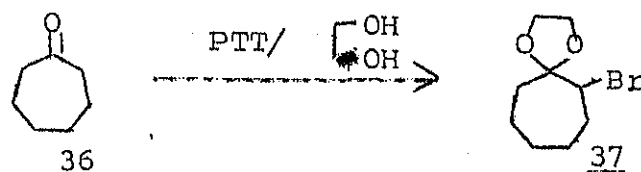
α -Bromoacetalization was carried out with 34 (4.9 g, 50 mmol), PTT (28.2 g, 75 mmol) and ethylene glycol (40 mL) in tetrahydrofuran (40 mL) for 27 h to yield 9.8 g of 35 (89%), b.p. 90-92°C

(5 mm), [lit.⁵ b.p. 115-116°C (10 mm)].

IR (thin film): 1150, 1130, 1080 ($\nu_{\text{C-O-C}}$).

PMR (CDCl_3): 1.16 - 2.46 (m, 8H, $-\text{CH}_2-$); 4.03 (m, 5H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$, $-\text{CH}-\text{Br}$).

II.B.4.8 α -Bromoacetalization of Cycloheptanone (36)



The reaction was carried out as earlier with 36 (3.18 g, 30 mmol), PTT (12.4 g, 33 mmol) and ethylene glycol (30 mL) in tetrahydrofuran (30 mL), for 30 h which yielded 5.68 g of 37 (81%), b.p. 77-80°C (0.5 mm), [lit.³ b.p. 79-83°C (0.5 mm)].

IR (thin film): 1150, 1100, 1040 ($\nu_{\text{C-O-C}}$).

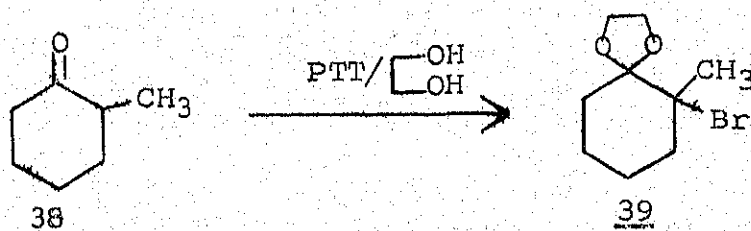
PMR (CDCl_3): 1.36 - 2.43 (m, 10 H, $-\text{CH}_2-$); 3.83-4.4 (m, 5H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$, $-\text{CH}-\text{Br}$).

MS (m/e): 236, 234 (M^+), 207, 205, 179, 177, 155, 113, 99, 86, 55.

Anal. for $\text{C}_9\text{H}_{15}\text{O}_2\text{Br}$: Calcd. C, 45.96; H, 6.38.

Found C, 45.62; H, 6.61.

II.B.4.9 α -Bromoacetalization of 2-Methylcyclohexanone (38)



The compound 55 (0.224 g, 2 mmol) was subjected to similar reaction conditions as in the earlier examples, using PTT (2.26 g, 6 mmol) and ethylene glycol (4 mL) in tetrahydrofuran (8 mL) for 28 h to give the crude product which was chromatographed over neutral alumina to yield 0.37 g of pure 39 (79%, elution with petroleum ether).

IR (thin film): 1175, 1100, 1040 ($\nu_{\text{C-O-C}}$).

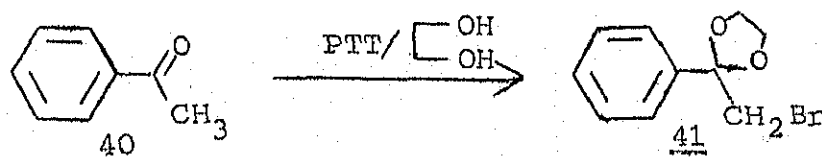
PMR (CDCl_3): 1.76 (s, 3H, $-\text{CH}_3$); 1.4 - 2.3 (m, 8H, $-\text{CH}_2$); 4.03 (s, 4H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$).

MS (m/e): 236, 234 (M^+), 169, 155, 113, 99, 86, 71, 57, 43.

Anal. for $\text{C}_9\text{H}_{15}\text{O}_2\text{Br}$: Calcd. C, 45.96; H, 6.38.

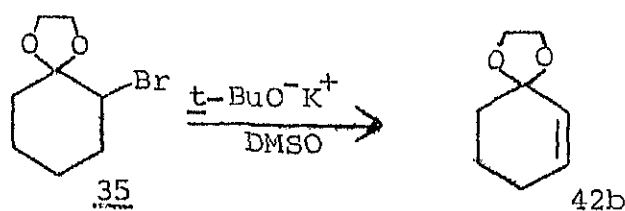
Found C, 45.69; H, 6.67.

II.B.4.10 α -Bromoacetalization of Acetophenone (40)



Treatment of acetophenone (40, 0.24 g, 2 mmol) with PTT (0.83 g, 2.2 mmol) and ethylene glycol (4 mL) in tetrahydrofuran (4 mL) for 22 h yielded 0.39 g of 41 (82%), m.p. 61°C (lit.⁷ m.p. 61°C).

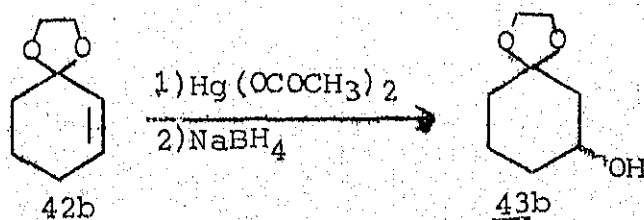
IR (CHCl_3): 1160, 1110, 1000 ($\nu_{\text{C-O-C}}$).

II.B.4.11 Preparation of Olefinic Acetal 42b

Potassium tertiary butoxide (8.84 g, 40 mmol) was taken in dry dimethyl sulphoxide (25 mL) and stirred at 40°C until a homogeneous solution was obtained. The bromoacetal 35 was added dropwise to the potassium tert-butoxide solution over 0.3 h and the stirring was continued for additional six hours. The reaction mixture was slowly added to cold water (125 mL) with stirring and extracted with hexane (4 x 100 mL). The hexane extract was washed with water (2 x 100 mL) followed by brine (100 mL) and dried over anhydrous magnesium sulphate. After filtering, the solvent was evaporated under reduced pressure to yield a liquid which was distilled to give 4.48 g of 42b (80%), b.p. 74-76°C (17 mm), [lit.³ b.p. 86.5-88.5°C (23 mm)].

IR (thin film): 1110, 1030 ($\nu_{\text{C-O-C}}$).

PMR (CDCl_3): 1.06 - 2.4 (m, 6H, $-\text{CH}_2$); 3.83 (s, 4H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$); 5.28-5.88 (m, 2H, vinylic).

II.B.4.12 Preparation of Hydroxyacetal 43b

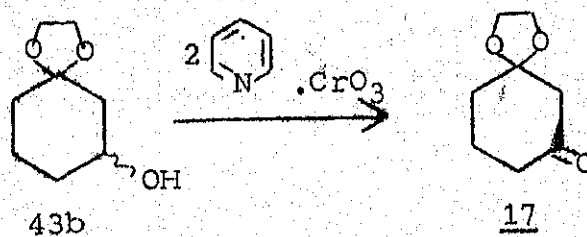
To a suspension of recrystallised mercuric acetate (2.8 g, 20 mmol) in acetonitrile containing water (80 mL, 95:5) was added the unsaturated ketal 42b in a small amount of acetonitrile, in one portion. The resulting mixture was stirred for 4 h during which the reaction mixture turned white and then it was cooled to 0°C. 10% aqueous sodium hydroxide solution (40 mL) was added followed by a solution of sodium borohydride (1.52 g, 40 mmol) in 10% aqueous sodium hydroxide solution (40 mL). The grey mixture was stirred at room temperature for 2 h, saturated with sodium chloride and filtered through a pad of celite and sand. The filtrate was extracted with a mixture of chloroform and ethyl acetate (1:1, 4 x 50 mL). The combined extract was washed with brine and dried over anhydrous magnesium sulphate. The solution was filtered and the solvent was evaporated under reduced pressure to afford an oil. The crude product upon flash chromatography yielded 2.12 g of the hydroxyacetal 43b (70%, elution with 1:1 ether-petroleum ether).

IR (thin film): 3400 ($\nu_{\text{O-H}}$), 1150, 1100, 1050 ($\nu_{\text{C-O-C}}$).

PMR (CDCl_3): 1.14-2.16 (m, 6H, $-\text{CH}_2-$); 2.9 (s, 1H, $-\text{OH}$, D_2O exchangeable); 4.0 (s, 4H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$).

MS (m/e): 158 (M^+), 141, 115, 99, 86, 71, 55, 43.

II.B.4.13 Preparation of Ketoacetal 17



To a solution of distilled pyridine (9.36 g, 120 mmol) in dry dichloromethane (100 mL) was added chromium trioxide (dried over phosphorus pentoxide, 6.0 g, 60 mmol) and clean dry celite (4 g). The resulting mixture was stirred at room temperature for 0.25 h. The hydroxyacetal 42b (0.948 g, 6 mmol) dissolved in dichloromethane (5 mL) was added to the burgundy red homogeneous solution of the reagent, in one portion. The reaction mixture turned black immediately and then it was stirred for an additional 0.25 h and then diluted with anhydrous ether, filtered through a pad of celite and sand. The celite cake was washed thoroughly with plenty of ether. The filtrate was evaporated to yield an oil which was filtered through a short silica gel column to afford 0.8 g of 17 (86%, elution with 3:7 ether-petroleum ether).

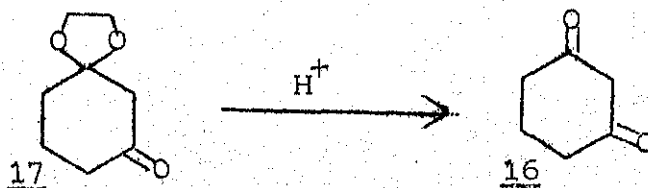
IR (CHCl_3): 1720 ($\nu_{\text{C=O}}$), 1120, 1090, 1020 ($\nu_{\text{C-O-C}}$).

PMR (CDCl_3): 1.66 (br, s, 4H, $-\text{CH}_2-$); 2.06 (br, s, 2H, $-\text{CH}_2-$); 2.26 (s, 2H, $-\text{CH}_2-$); 3.76 (s, 4H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$).

Anal. for $\text{C}_8\text{H}_{12}\text{O}_3$: Calcd. C, 61.53; H, 7.69.

Found C, 61.3; H, 7.8.

II.B.4.14 Hydrolysis of 17 with Acid Impregnated Silica gel

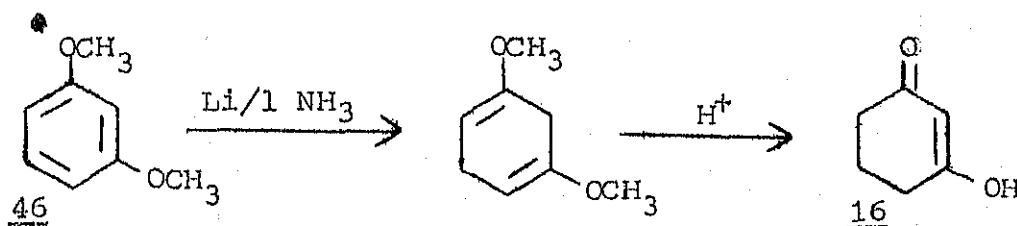


To a suspension of silica gel (100-200 mesh, 3.0 g) in dichloromethane added 15% sulphuric acid (0.6 mL) and stirred

until the turbidity in the dichloromethane vanished. Added keto-acetal 17 (0.5 g, 6.4 mmol) in a small amount of dichloromethane in one portion and stirred for 24 h. Solid sodium bicarbonate was added with stirring until no effervescence was observed. Filtered the reaction mixture and washed the silica gel residue thoroughly with dichloromethane. The filtrate was evaporated to give 0.55 g of 16 (78%), m.p. 105-106°C (lit.²¹ m.p. 105-107°C).

IR (CHCl₃): 3400 ($\nu_{\text{O-H}}$), 1705 ($\nu_{\text{C=O}}$), 1660, 1620 ($\nu_{\text{C=C-O}}$).

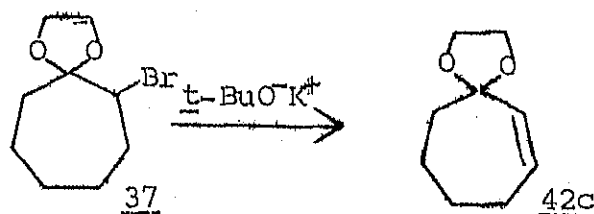
II.B.4.15 Preparation of Dihydroresorcinol (16)



Lithium pieces (6.9 g, 100 mmol) were added in portions to liquid ammonia within ten minutes. A solution of resorcinol dimethyl ether (2.76 g, 20 mmol) in anhydrous tetrahydrofuran (15 mL) and absolute ethanol (2.2 mL) was added slowly dropwise to the blue solution and stirred for 1 h during which the reaction mixture turned white. Solid ammonium chloride was added to destroy excess of lithium and the ammonia was allowed to evaporate at room temperature. The curdy white paste was taken in water and extracted in ether (3 x 50 mL). The ether extract was washed with water several times followed by 10% aqueous sodium hydroxide solution (50 mL) and then with brine. The ether extract was dried over anhydrous sodium sulphate, filtered and concentrated

to afford 1.9 g of an oil (47, 68%), b.p. 94-95°C (18 mm) [lit.⁴¹ b.p. 95°C (18 mm)]. A solution of 47 (1.4 g, 10 mmol) in dichloromethane was shaken with concentrated hydrochloric acid (1 mL) for 0.25 h. The organic layer was stirred with solid sodium bicarbonate, filtered, dried over sodium sulphate and evaporated to yield 0.9 g of 16 (60%), m.p. 105-106°C (lit.²¹ m.p. 105-106°C).

II.B.4.16 Preparation of Olefinic Acetal 42c

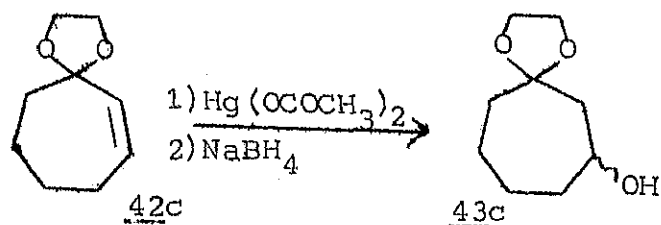


Potassium tert-butoxide (3.36 g, 30 mmol) was dissolved in dry dimethyl sulphoxide (20 mL) at 40°C. To the resulting solution, 37 (4.7 g, 20 mmol) was added slowly dropwise at room temperature and stirred for 4 h. Poured the reaction mixture slowly into cold water and extracted with hexane (3 x 50 mL). The hexane extract was washed several times with water followed by brine and dried over magnesium sulphate; filtered and the solvent was removed under reduced pressure to yield 2.15 g of 42c (70%), b.p. 94-96°C (10 mm) [lit.³ b.p. 67°C (2.4 mm)].

IR (thin film): 1100, 1070 (ν_{C-O-C}).

PMR ($CDCl_3$): 1.4-2.5 (m, 8H, $-CH_2-$), 3.8 (m, 4H, $-O-CH_2-CH_2-O-$), 5.66 (m, 3H, vinylic).

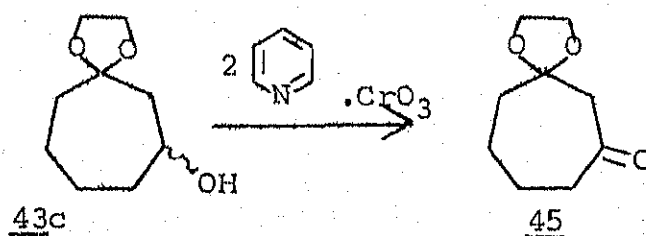
II.B.4.17 Preparation of Hydroxyacetal 43c



To a suspension of mercuric acetate (4.0 g, 12.6 mmol) in tetrahydrofuran-water (1:1, 20 mL) was added the unsaturated ketal 42c (1.84 g, 12 mmol) and stirred for 2 h during which the reaction mixture turned white. To the resulting mixture at 0°C, added 10% aqueous sodium hydroxide solution (12 mL) followed by a solution of sodium borohydride (0.91 g, 24 mmol) in 10% aqueous sodium hydroxide solution. The usual work-up as given in II.B.4.12 afforded an oil which was purified by flash chromatography to give 1.32 g of 43c (64%).

IR (thin film): 3380 (ν_{OH}), 1100, 1070 ($\nu_{\text{C-O-C}}$).

II.B.4.18 Preparation of Ketoacetal 45



The reagent 2Py.CrO₃ was prepared using pyridine (7.8 g, 100 mmol) and chromium trioxide (5 g, 50 mmol) in dichloromethane (80 mL) along with celite (3 g). A solution of 43c (0.86 g, 5 mmol) in dichloromethane (5 mL) was added in one portion and worked up after 0.25 h as given in II.B.4.13, to yield an oil

which upon flash chromatography yielded 0.609 g of 45 (70%, elution with 1:1 ether-petroleum ether).

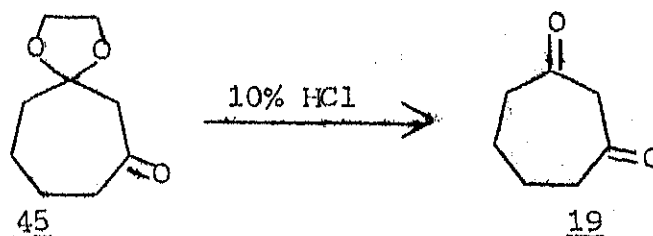
IR (CHCl_3): 1700 ($\nu_{\text{C=O}}$), 1080, 1040 ($\nu_{\text{C-O-C}}$).

PMR (CDCl_3): 1.66 (br, s, 6H, $-\text{CH}_2$); 2.23 (br, s, 2H, $-\text{CH}_2$); 2.56 (s, 2H, $-\text{CH}_2$); 3.76 (s, 4H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$).

Anal. for $\text{C}_9\text{H}_{14}\text{O}_3$: Calcd. C, 63.52; H, 8.23.

Found C, 63.20; H, 8.50.

II.B.4.19a Hydrolysis of 45 with 10% Hydrochloric Acid

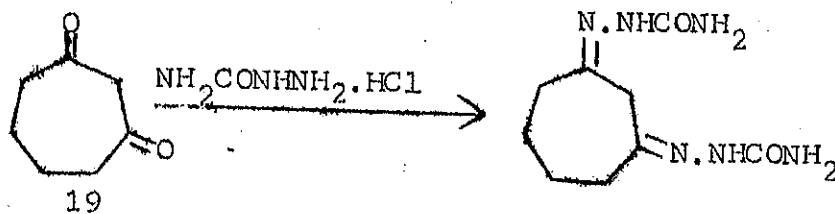


The compound 45 (0.5 g, 3.96 mmol) was stirred with 10% hydrochloric acid (10 mL) for 2 h at room temperature. Extracted with chloroform (5 x 20 mL) and the organic layer was washed with saturated sodium bicarbonate solution (20 mL) followed by water (20 mL) and then brine (20 mL); dried over anhydrous magnesium sulphate, filtered and concentrated to yield an oil which was filtered through a short pad of neutral alumina (elution with 3:7 ether-petroleum ether) to afford 0.374 g of 19 (75%) as a liquid.

IR (CHCl_3): 1710 (split, $\nu_{\text{C=O}}$).

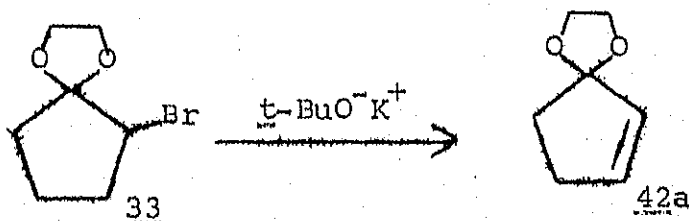
PMR (CDCl_3): 1.33 - 2.1 (m, 4H, $-\text{CH}_2$); 2.46 (m, 4H, $-\text{COCH}_2$); 3.53 (s, 2H, $-\text{COCH}_2\text{CO}-$).

II.B.4.19b Preparation of Disemicarbazone of 19



To a solution of semicarbazide hydrochloride (0.166 g, 1.5 mmol) and sodium acetate (0.122 g, 1.5 mmol) in water (5 mL) was added a solution of 19 (0.063 g, 0.5 mmol) in ethanol (2 mL). The resulting mixture was heated on a water bath for 0.5 h. Colourless crystals separated out on cooling which were filtered and dried to yield 0.1 g of the disemicarbazone of 19 (90%), m.p. 204–206°C (dec.) [lit.²³ m.p. 205–206°C (dec.)].

II.B.4.20 Preparation of Olefinic Acetal 42a



The dehydrobromination reaction was carried out as earlier with 33 (4.14 g, 20 mmol) using potassium tert-butoxide (3.36 g, 30 mmol) in dimethyl sulfoxide (15 mL) to yield 1.96 g of the unsaturated ketal 42a, b.p. 64–66°C (21 mm) lit.³ b.p. 65–66.5°C (22 mm).

IR (thin film): 1620 ($\nu_{\text{C}=\text{C}}$), 1080, 1050, 1025 ($\nu_{\text{C}-\text{O}-\text{C}}$).

PMR (CDCl_3): 1.48–2.56 (m, 4H, $-\text{CH}_2$); 3.84 (s, 4H, $-\text{CH}_2$), 5.56–6.08 (m, 2H, vinylic).

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VITAE

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